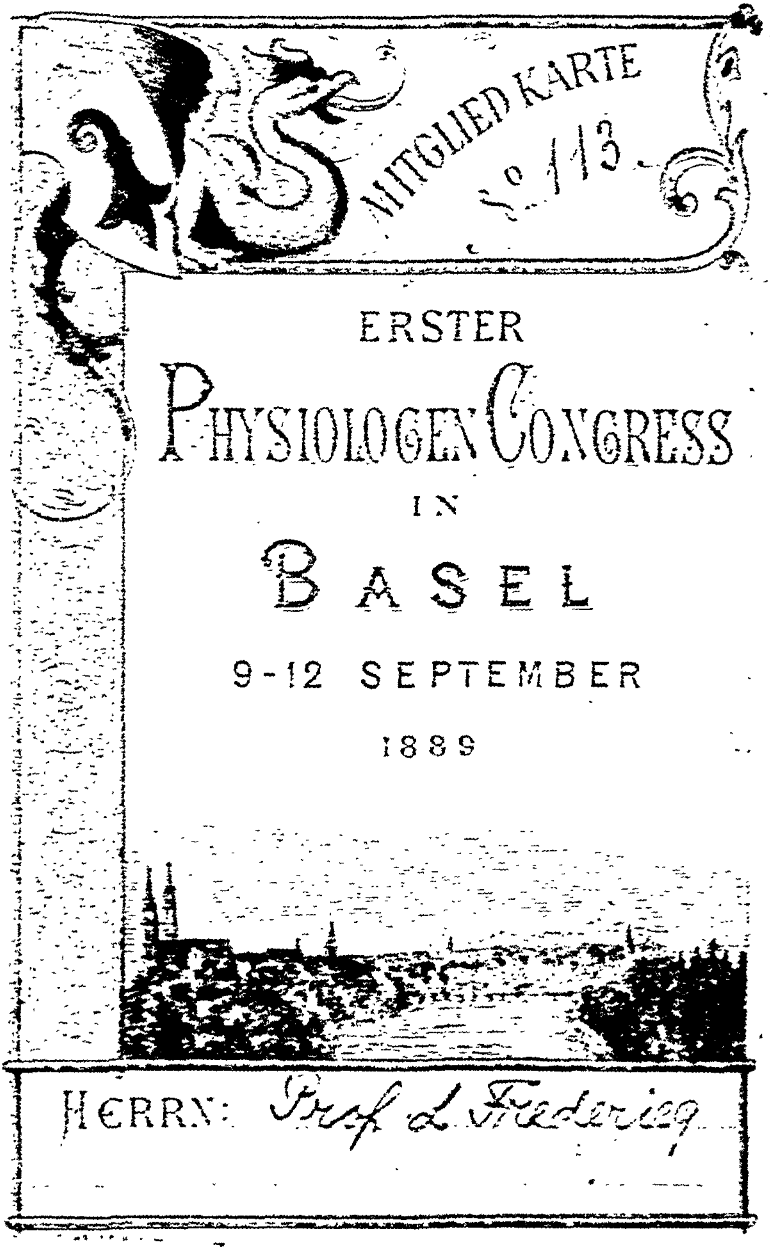
A SHORT HISTORY OF PHYSIOLOGY



Membership card, issued to Léon Fredericq, of the first International Congress of Physiologists, Basel, 1889. Original preserved at Liège. Courtesy of Professor Henri Fredericq.

A SHORT HISTORY OF PHYSIOLOGY

BY

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SECOND EDITION

"He who wants fully to command a science must also know its evolution, its 'embryology'."

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PREFACE TO THE FIRST EDITION

In preparing this book I have consulted works by so many authors that I cannot mention them all for lack of space. Among these writers are Langdon Brown, Sir Thomas Barlow, Pan Codellas, A. E. Cohn, C. Dobell, Franklin Fearing, J. Finlayson, Sir Michael Foster, J. F. Fulton (who has also helped me in person), Fielding Garrison, H. Hopstock, E. C. van Leersum, Graham Lusk, L. L. Mackall, J. P. McMurrich, Sir William Osler, T. S. Patterson, Sir D'Arcy Power, J. S. Prendergast, F. Prescott, Sir Charles Sherrington, Charles Singer and Jules Soury. To them, and to the many others whom I have not mentioned by name, I am indebted for all that is good in the book; its imperfections I prefer to acknowledge as my own. If readers find any mistakes, or would like to offer suggestions, I should be glad to receive letters from them.

It may, with some reason, be alleged that I have given too long an account of the work before Harvey, too short an account of the work done after his time. It seemed to me, however, that the physiological thought of two thousand years should not be compressed into too small a number of pages, for readers would tend to forget the slowness of progress during these centuries, if the account were made too brief.

If they will permit me to do so, I should like to dedicate this short history of physiology to my past and

present pupils. I am sure that no teacher of the subject has more pleasant memories than I have of those whom he has taught, and I should like to present the book to them with my best wishes for every success in their future careers. Three of my ex-pupils, E. H. Leach, R. E. Johnson and J. Walter, kindly suggested certain minor alterations in the manuscript.

K. J. FRANKLIN

Oriel College, Oxford.
September, 1933.

PREFACE TO THE SECOND EDITION

Thanks to the collection of relevant material over a number of years, I was able to write the first edition of this book in a very short space of time, and in consequence it possessed a continuity of thought and treatment which I trust it has not lost through the textual re-casting required for this second edition. The major changes which I have introduced are of my own making, and they incorporate extra information which has become available in the intervening years; for certain other additions, however, and for the elimination of some minor errors, I am indebted to Professor C. Lovatt Evans, Professor J. A. Gunn, Professor J. M. D. Olmsted, Dr. F. H. Pratt, and other friends. In this second edition, as in the first, I have stopped short of the twentieth century because it would be invidious for me, as a practising physiologist, publicly to assess the work of others still alive. If, however, a third edition is called for, I may consider adding, without comments, a chronological list of publications and researches which have influenced progress from 1900 onwards. I have one such partly prepared, but I should be grateful for suggestions as to items, worthy of inclusion, which I may be in danger of overlooking.

The first edition appeared in an unattractive format, with no title on the spine of the book, and no illustrations. Presumably, the object of all this was to keep the

price as low as possible, but in the view of my new publishers (a view with which I myself concur) such parsimony defeated the real object of the book. This second edition, therefore, costs considerably more but it is hoped that the greater elegance of its production, and the introduction of a frontispiece and sixteen other figures, will more than compensate for the increase in price.

I trust that, in its new format, the book will continue to arouse interest in the fascinating science to which it is an introduction, and I place here the quotation that was on the title-page of the first edition, namely, "He who calls what has vanished back again into being enjoys a bliss like that of creating". For that sentiment expresses well the pleasure which I have experienced in the making of my brief survey.

One last point which I should mention here is that Arabic names (e.g. Ibn an-Nafis) have been printed throughout in their anglicized form. Those readers who wish to be more scholarly in this respect can consult the article, by Max Meyerhof, to which reference is made in chapter II.

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London, E.C.1.
October, 1947.

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The word "physiology" itself has undergone many changes of connotation. Originally it meant an inquiry into nature, especially into the origin and nature of things. Later it lost this more philosophical character, and became rather the study and description of natural objects and phenomena. Then, in 1554, Jean Fernel used the word as a substitute for what he had, in 1542, styled *naturalis pars medicinae;* in its scope he included the normal structure and functioning of the human subject, but his treatment of the functioning, if more systematic than previous accounts, was — like them — highly theoretical. Fernel's book was immediately popular, and it continued to be reprinted long after his death; it can, therefore, be presumed that many employed the term "physiology" in the way that he had done; indeed, there is direct evidence that his publication did have such an effect. But simultaneously the older usage also persisted, e.g. William Duncan's *Physiologia* of 1651 contained a section on metals and precious stones. In the middle of the eighteenth century, thanks largely to Haller and a few others, a purely biological connotation became widely or even generally accepted, and "physiology" included the study of human structure and function, together with a fair amount of comparative work. The functional aspects, however, still derived in considerable part from structural considerations, and Purkinje later described the physiology

of this century as just a commentary on anatomy. In John Hunter's time and at the beginning of the nineteenth century, there was an even greater inclusion of comparative anatomy in physiology; indeed, right up into the present century the Physiological Curator at the Hunterian Museum of the Royal College of Surgeons of England was the person in charge of the section of comparative anatomy. On the other hand, particularly in France, studies of animal function at the beginning of the nineteenth century began to include more and more the results of animal experiment, and "physiology" began to change its connotation to correspond. To the new method of approach, in part, was due the separation of physiology from the gross and comparative structural studies on which it had for so long, in so large a measure, been based. But it was not everywhere that experimental work stimulated the divorce. In some places, after the intimate cellular structure of the body had become known (*c.* 1830 onwards), the most exciting laboratory work giving rise to new ideas of functioning was the detailed microscopic examination of the tissues. So in certain situations the main research interest of the physiologist was histology*. Indeed, the first physiological Institute was that which was built for Purkinje in Breslau; it was opened in October, 1839. For his time, Purkinje had a wide concept of the scope of physiology, but he included much that was anatomical (despite his remark about eighteenth century physiology), and to-day his

* The association of the two subjects, in so far as teaching is concerned, persists to this day in many medical schools; in most, if not all, of these practical histology was introduced into the students' course long before practical physiology became a routine class exercise.

name is particularly associated with *histological* discoveries. From all the above, it is clear that the limitation of the term "physiology" to knowledge, gained by scientific means, of the normal functioning of organisms, or of their constituent parts, is an innovation of the last hundred years. The present volume will deal with the history of *animal* physiology; it will show first the evolution of the experimental method, and then the results which have in more recent times attended its use.

CHAPTER I

THE RISE OF PHYSIOLOGY IN THE ANCIENT WORLD

> *"Man can do a great deal by observation and thinking, but with them alone he cannot unravel the mysteries of nature."* — OSLER.

MANY of the pertinent writings of the ancients have been lost, and the correct interpretation of those that remain is difficult at this distance of time. If, however, we select a few of the contributions which were made to physiological thought between the sixth century B.C. and A.D. 200 we may be able to obtain at least some impression of the whole.

Alcmaeon of Croton, who flourished in the latter half of the sixth century B.C., was one of the first to express views on the functions of the body. It is not known if these were to any material extent based upon experiment. Alcmaeon was one of the first among the Greeks to localize perception of sensations and thought within the brain. He stated that man differs from lower animals because he alone comprehends as well as perceives. He was keenly interested in the special senses; he thought that the eye contained fire, as a blow upon it produces flashes; he explained hearing as due to the resonance of the aural cavity, and taste as dependent upon the moisture, warmth and supple character of the tongue. Smell was due to the brain drawing up

Alcmaeon of Croton

the air and its contained savours through the nostrils. Health was the result of an evenly proportioned balance of qualities; sleep was produced by the retreat of blood to the blood-carrying veins, and awakening by its pouring forth; death was due to the total retreat of the blood to the same vessels. On the other hand, he thought that goats breathed through their ears! One important fact about Alcmaeon is that he used the word "pores" for the nerves, and in this was followed for a long time by his successors. How far this was responsible for the idea that nerves were hollow tubes it is not possible to say, but this view of nerve structure persisted long after the discovery of the circulation, and had important bearings on physiological thought.

Hippocrates

Hippocrates of Cos (*c.* 460 B.C. to 377 or 359 B.C.), the father of medicine, was not a physiologist, though he knew the heart had valves and called it a very strong muscle. He did, however, demonstrate the value of clear observation and of terse and accurate description, and his methods of treatment show that, even if unconsciously, he recognized within the body a physiological tendency to health.

Aristotle

After Hippocrates, the accurate observer of diseased man, came Aristotle (384—322 B.C.), the careful observer of animal life, and one of the greatest of natural historians. His influence upon Alexander the Great, whom he tutored for six years, led indirectly to the development of the medical school at Alexandria, in Egypt. Aristotle is of interest to our story in that he was a pioneer in natural history and embryology. He was also the first to *illustrate* a biological treatise, though his drawings are lost. His chief object of embryological research was

the developing chick, and it remains a popular one to this day. He differentiated the classes of animals on anatomical, physiological, and embryological grounds, knew the important features of mammals, and placed the Cetacea among or near them, thus anticipating conclusions of two thousand years later. He thought that the generation of most animals needed the participation of two sexes, and that the egg was rendered capable of development by the sperm of the male. On the other hand, he believed in the spontaneous generation of some forms, an idea which was only finally refuted by Pasteur. He considered that the soul (psyche) differentiated living and non-living substance, and that its activity resulted in form. Of this living principle he distinguished three types, the lowest concerned with nutrition and reproduction, the next with sensation, and the highest with intellect. Life, existing in matter, he defined as the power of self-nourishment and of independent growth and decay. Probably because he had found experimentally an irresponsiveness of the brain, he regarded the heart as the seat of intelligence, and the brain as an organ for cooling the heart by the secretion of pituita. With regard to the blood vessels, he said that as they "advance, they become gradually smaller and smaller, until at last their tubes are too fine to admit the blood". Aristotle was an observer rather than an experimenter, and so was a forerunner rather than an exponent of physiology.

After embryology, anatomy! This subject was first placed on a definite footing by Herophilus of Chalcedon at Alexandria in the third century B.C. In physiology, Herophilus recognized the brain as the central organ of the nervous

Herophilus

system, and he regarded it as the seat of intelligence, reversing thus the view of Aristotle. He was the first to grasp the nature of the nerves, which he distinguished as concerned with motion and sensation. He differentiated arteries and veins, though in this he had been anticipated by Praxagoras of Cos about 335 B.C.; he was also the first to count the pulse, and to make a detailed analysis of its variations; this he did with the aid of a water-clock.

Erasistratus

Erasistratus of Chios, somewhat the junior of Herophilus, was the second great figure of the Alexandrian school. He has been called the father of physiology, but others give this title to Galen, who went much farther in animal experiment and who was not, like Erasistratus, content to deny a function to certain organs (e.g. the spleen). It is not easy, in any case, to give an exact account of the work of Erasistratus, as this has to be deduced chiefly from Galen's writings. He had a good knowledge of the anatomy of the heart and described the trachea, atria, cardiac valves and chordae tendineae. He is said to have differentiated the anterior spinal roots as motor in function, the posterior as sensory. He also devised the first crude metabolism experiments, attributed the feeling of hunger to emptiness of the stomach, and recognized the action of skeletal muscles in the mechanism of movement. The diaphragm was, he thought, the only muscle concerned in respiration. Finally, he associated the higher intelligence of man with the greater elaboration of his cerebral convolutions. So far so good, but, like all the ancients, he had to produce a general plan of the body's working and this had to be largely theoretical. Erasistratus was a materialist and ration-

alist, and he accepted the atomism of the philosopher Democritus (*c.* 470—380 B.C.). He regarded nature as an external power acting on the body.

The basis of his physiology, according to Singer, was the observation that every organ has a threefold system of vessels: arteries, veins and hollow nerves. In these three kinds of tubes were found blood and two sorts of "pneuma" (breath or spirit). These last were imaginary, and pneumatism can be traced back to the Hippocratic school; it was, however, to play an important part in retarding the development of physiology for centuries, so it is necessary to say more about it. Undoubtedly the idea at the back of the pneuma was in part an explanation, however imperfect, of the need of respiration for life, but it became elaborated to fill up gaps in experimental knowledge of this and of other parts of physiology. A further point, which probably misled the ancients, e.g. Aristotle, was the fact that after violent death the liver, veins and right heart are congested with blood, while the left heart and arteries are relatively empty. The explanation which Erasistratus gave to account for this was that the blood is present in life in the liver, veins and right heart alone, the arteries containing none. Air taken in by the lungs is changed in the left heart into a peculiar pneuma, the vital spirit, and this is carried in the arteries to all parts of the body, including the brain. In the brain it is further changed into a second pneuma, the psychic spirit, which is distributed to all parts by the hollow nerves. Erasistratus got over the fact that arteries bleed on being cut by saying that the escape of pneuma allowed a vacuum to form, and that blood flowed in from the veins through [hypothetical] anastomoses,

which became patent only under such abnormal conditions.

Galen, the last of the ancients whom we shall consider, and whose writings were destined to dominate medicine for over a thousand years, was born at Pergamum in A.D. 130, when the Roman Empire was at the height of its power. At fifteen he commenced the study of philosophy and at eighteen that of medicine, and he combined both for the rest of his life. He travelled to Smyrna, Corinth and Alexandria, where "the science of physiology did not prosper. It was in bondage to the memory of the greatness of Erasistratus". After four more years in Pergamum, he set out for Rome (A.D. 161), and soon established himself in the capital. It was not long before he was physician to the Emperor, Marcus Aurelius, and his lectures on anatomy and physiology were frequented by the leaders of society. He died about A.D. 200.

Galen

Galen was a strange mixture. Though his name means "Peaceful", he inherited a haughty and overbearing temperament. He had that feeling of intellectual superiority which was so common among the Greeks, though one must admit that in his case it had much justification. His chief fault, however, was that he believed himself acquainted with the "final cause" of nature, the reason why things are as they are. By arrogating to himself such divine omniscience he marred his real greatness. His belief was that God had made all the organs of the body as perfect as possible for their functions; he was not therefore so concerned with the "efficient cause", i.e. how the parts of the body work.

The object of physiological research is to discover, by mainly experimental methods, how living beings perform their various functions. If experiments are planned with care and skill, if fortune is with the physiologist, and if he interprets the results of his experiments without any bias, he will be able to make contributions of worth to his science. If, however, like Galen, he considers that he already knows the general scheme of nature, he will be much more liable to error, less enthusiastic, and less likely to advance his subject. Galen was an operator of consummate skill and ingenuity, but his experiments would have carried him to greater fame if he had had no preconceived notions of nature's processes. He made many important discoveries which aided physiology, but he also left many ideas which retarded its development after him. Before analysing these, it is only right to note that he was the first to link up clinical observations with anatomy and physiology (i.e. to seek an explanation of pathological conditions in disorders of normal structure and function), and to say that he collected and synthesized all the medical knowledge of his predecessors. For these two things alone he would deserve our gratitude!

The advances which he made in physiological knowledge form an imposing list. In the physiology of the neuro-muscular system he showed, by experiments on primates and lower mammals, that longitudinal section of the cord causes no muscular paralysis, whereas transverse section causes complete loss of sensation and power of muscular movement below the level of the lesion. Semisection causes muscular paralysis solely on the side of the lesion. He realized the segmental innervation of various muscles, and demonstrated the origin

and function of the phrenic nerve. He knew that the diaphragm was not the only muscle concerned in respiration, and he showed the parts played respectively by it, the intercostals and the accessory muscles. He discovered the function of the recurrent laryngeal nerve, and at will stopped the cries of animals by tightening a ligature placed round this nerve. He said that sound was due to air vibrations, spoke of the antagonistic action of muscles and of muscle tone, and differentiated voluntary from involuntary muscles. He believed in the intrinsic nature of the heart beat, and made important observations on the functions of the oesophagus, stomach, intestines and bladder. He knew of insensible perspiration. He observed the heart in situ with the thorax open but with both pleurae uninjured, and saw that both ventricles pulsate. Erroneously, he thought that cardiac and arterial diastoles were simultaneous. He disproved the view of Erasistratus that the left heart and arteries are empty of blood. In the case of the latter, he tied off a section of an artery and opened it to find it full of blood; obviously there was no anastomosis of this portion with any vein. He proved this fact for various arteries, both deep and superficial. His other views on the functioning cardiovascular system will be considered after an analysis of his general idea of the body's working.

Galen postulated three pneumata where Erasistratus had only two. The foodstuffs were taken as chyle from the alimentary canal to the liver, and there changed into blood. The lowest pneuma, the natural spirit, was localized in the liver, veins and right heart, and with the ebb and flow of the venous blood was distributed to all parts of the body. In the lungs this blood

was purified by the discharge of fuliginous vapours. The dynamic manifestation of this natural spirit, the natural force, was concerned with sensual desires, nutrition and blood formation. It served thus for the nutrition and growth of the individual and of the species. The second pneuma, the vital spirit, was localized in the left heart and in the arteries; it was produced by the interaction of air (brought in from the lungs through the pulmonary vein) with blood which passed from the right side of the heart to the left through minute pores in the interventricular septum. The dynamic manifestation of this vital spirit, the pulsatile force, was concerned with courage, anger, personality and bodily heat. It served thus to ensure the activity of the heart, the production of heat in the left ventricle, and its distribution by the arteries; its auxiliary functions were connected with respiration and with the pulse. Some of this blood in the arteries reached the brain and in the ventricles of that organ was produced the third pneuma, or psychic spirit. This spirit was localized in the brain and nerves, and its dynamic manifestation, the psychic force, was concerned with intellectual activities, sensation and movement. Intellectual activities were imagination, the power of thought and memory. Sensation included vision, smell, taste, hearing and touch. Galen appears to have given the different functions differential localization in the brain, thus abolishing the *sensorium commune* of Aristotle. The psychic spirit, finally, was only the chief agent of a soul (psyche) located in the brain substance, and served for the distribution throughout the body of the powers of sensitivity and movement.

The schema is a remarkable piece of constructive

thought to account for the physiology of the whole body, but it was destined to do incredible harm to the progress of physiology, because more stress was laid upon it than upon Galen's experimental work, and physiology cannot grow in an atmosphere of dogma, however ingenious that dogma may be.

The doctrine of the transmission of a very small amount of venous blood through invisible pores in the interventricular septum to the left heart was Galen's logical deduction from the finding of blood in the arteries, at a time when no communication was known to exist between the pulmonary artery and vein. Galen thought that the right atrio-ventricular opening was wider than the pulmonary artery, and that the left atrio-ventricular opening was narrower than the aorta; this led him to postulate transference of some blood through the septum, and this one assumption, unsupported by experimental proof, held up physiological progress for centuries.

With this account, however imperfect for lack of space, we must leave the ancients. After Galen, for over a thousand years, physiology, in common with other intellectual activities, showed a retrogressive tendency. The rise of Christianity, with its insistence on spiritual things, did nothing to help medical science; the practical spirit of the Roman Empire was not calculated to advance pure science; finally, the downfall of the empire and the barbarian invasions completed the adverse influences.

That Galen's works survived and, even in mutilated form, became authority itself in medicine was due to various causes. Christianity had been kindly referred to in some of his works and his views of a single deity,

who had made every organ perfect for its function in the body, made him acceptable to the devotees of the new religion. His comprehensiveness and self-confidence must also have inspired no small degree of acceptance.

Entirely apart from general causes, however, there were certain special ones why physiology did not progress for a long time after Galen. Anatomy is the localizing basis of physiology, and the knowledge of anatomy, though not inconsiderable, was insufficient for the purpose of appreciating function. The systematic anatomical treatment of a single species or order was non-existent in Galen's time — it had to await Vesalius. Further, the anatomy of the day dealt, as Wotton stated, with the *containing* parts (skin, bones, muscles, arteries, veins, bowels, etc.), and not with the *contained* parts (bone-marrow, blood, serum, digestive juices, etc.). Investigation of these latter had to wait upon physics and chemistry and upon various instrumental discoveries. There was also no continuity in teaching as we know it to-day. More difficulty was experienced in intercommunication and travel, and transcription of manuscripts was no satisfactory equivalent of the printing that was to come. In general, too, the art of illustration was non-existent, and its value to anatomy cannot be over-emphasized. Physiology also suffered in other ways than through lack of a systematic anatomy. It was not recognized as a separate entity, and was represented chiefly by theories, and only in part by experimental fact. Rules for a concerted attack upon its problems were unformulated, and principles of criticism and research, which we can now draw from its historical study, were entirely absent. The idea of control experiments, as we know

it, was not yet evolved. Neither of the two guiding principles in physiology, the integrative action of the circulatory system and the integrative action of the nervous system, was present to give order to the facts that had been already elucidated. Physiology is born of an exact knowledge of anatomy and a correct application of the experimental method, and this first product of their conception was a weakling because of the immaturity of both parents.

CHAPTER II

IBN AN-NAFIS (*c.* 1210—1288)

BETWEEN Galen's time and that of William Harvey (1578—1657), the most interesting contributions were:

(1) Views about alternative blood pathways (i.e. pathways other than direct ones through the interventricular septum) from the right side of the heart to the left side. The first such view, which is described in this present chapter, was that of Ibn an-Nafis. The later ones were those of Servetus (1553), Columbus (1559), Botallus (1564), and Caesalpinus (1571 and subsequently), and they are dealt with in chapter VI. For four of these five writers the alternative pathway was via the pulmonary artery and pulmonary vein; for the fifth (Botallus) it was from atrium to atrium via a patent foramen ovale. None of the accounts described a blood circulation in our sense, though we owe the actual word "circulation" to Caesalpinus.

(2) The views and physiological demonstrations of Leonardo da Vinci (1452—1519). These were not published at the time, so their main interest is the evidence they provide of the waning deference to traditional views and of the revival of demonstrations in the living animal (see chapter III).

(3) The publications of Jean Fernel (1497—1558) who, imbued with the renaissance spirit, did what was

possible, without experimental work, to enliven and systematize physiology, and who was the first to employ the word "physiology" in its more modern and restricted connotation (see chapter IV).

(4) The anatomies of Vesalius (1514—1564) and of others, and the physiological demonstrations devised by Vesalius (see chapter V).

(5) The discoveries of the valves in veins (see chapter VII).

These five contributions were evidence of dissatisfaction with authority and of readiness to put forward new views and new facts, i.e. they were signs of healthy, if slow, progress in anatomy and physiology. On the other hand, the last two items far transcended the first three in their ultimate importance to our story.

Knowledge of the contribution made by al-Qurashi, called Ibn an-Nafis (*c.* 1210—1288), has only recently become available through the researches of an Egyptian physician, Muhyi ad Din at-Tatawi (*Thesis*, Freiburg, Breisgau, 1924) whose findings were confirmed and extended by Max Meyerhof (see *Isis*, 1935, *33*, 100—120). According to the latter, the most important medical events of the twelfth century A.D. were the foundation of the Nuri Hospital in Damascus and the construction of the Nasiri Hospital in Cairo. Ibn an-Nafis was a highly learned Doctor from Damascus, who for a while was in charge of the great Nasiri Hospital and also for some time Chief of the Physicians in Egypt.

It was in his *Commentary on the Canon of Avicenna* that he produced his new ideas about the passage of blood from the right to the left side of the heart; briefly, they were as follows. The pores in the interventricular

septum are closed ones and the cardiac substance there is thick. So there is no visible communication between the two heart chambers, as thought by some persons, or an invisible communication permitting the passage of blood, as alleged by Galen. Indeed, the septum is specially thick in order to prevent the direct passage of blood or spirit from ventricle to ventricle, for this might be harmful. What actually happens is that blood is heated and refined in the right ventricle, and in consequence rises up in the artery-like vein [the pulmonary trunk and its branches] to the lungs, where part of it is further refined by its transudation through the thick walls of the vein in question, the less refined part serving for the nutrition of the lungs themselves. The clearest and most refined fraction, plus considerable airy substance, passes back to the heart after penetrating through the thin walls of the vein-like artery [the pulmonary venous system], and in the left ventricle its further admixture with the air, brought with it from the lungs, gives it the necessary aptitude for the production of the vital spirit.

In addition to the above, Ibn an-Nafis stated that there are perceptible passages or pores between the artery-like vein and the vein-like artery; the pores in the artery-like vein are very close so that only very refined blood may transude from it. Finally, at the end of his considerations of the anatomy of the heart, he contended that the right ventricle has no active movement and that it is a matter of indifference whether one calls the heart a muscle or not.

Obviously, Ibn an-Nafis cannot be said to have discovered the pulmonary circulation; even if he did adumbrate in some measure its pathway, he allowed

only a small amount of the right ventricular blood to make the circuit, and he made the right ventricle inactive. What he did do was to deny a direct interventricular communication; he had, therefore, to find an alternative pathway for a small amount of blood which had to be mixed with air in order that the vital spirit could be produced in the left ventricle. A very long time was to elapse before it became a practice of investigators to separate their observed facts from their hypotheses and ideas; indeed, quite a considerable time had to elapse before the former began to preponderate at all over the latter.

In the absence of any concept of a blood circulation in our modern sense, the main contribution of Ibn an-Nafis was, therefore, to emend an incorrect point in cardiac anatomy. It seems unlikely that his views exerted any marked influence, for there was no direct transmission of them to Servetus, who gave a somewhat similar account of the pulmonary blood pathway three centuries later; in addition, scepticism about an interventricular passage for the blood had similarly to reappear, as if de novo, in the sixteenth century (see chapter V).

CHAPTER III

LEONARDO DA VINCI (1452—1519)

"A modern biologist in the guise of a mediaeval artist." — HOPSTOCK.

LEONARDO DA VINCI, the great Italian, left a number of drawings and notes, the full significance of which was not appreciated until long after his day. Nor can one say that they had any marked influence on the progress of physiological thought, for they did not become common property. They are, nevertheless, of such interest that it is worth while to devote some space to them, and to their author.

Da Vinci's medical sources were chiefly the Arabic derivatives of the classical writings, but he was not overawed by authority. He dissected the bodies of men and of animals, and was the first after Aristotle to recognize the scientific value of accurate illustration. The combination of artist and anatomist which he exhibited has probably never been equalled. "If the impulse to the new anatomy came from the artists, Leonardo may well be recognized as its originator and Vesalius as its great protagonist." Da Vinci was a firm believer in observation and experiment and, whenever possible, preferred to explain a phenomenon as resulting from natural causes. He believed that no human findings could be termed true knowledge if they did not proceed to mathematical demonstration. He held teleological views not unlike those of Galen and stated that

"nothing is superfluous and nothing lacking in any kind of animal and product of nature." His physiology was in many respects an advance on that of Galen, though it retained much that was galenic. In respiration he stated that the lungs expand and contract continuously in all directions, but chiefly downwards. The lung, which touches the ribs on their inner surface, must follow them in their movements. The diaphragm is primarily a respiratory muscle, but by its pressure helps to push the gastric contents into the intestine; it also acts with the abdominal wall in the act of defaecation. As a result of his experiments on inflation of the lungs, he concluded that it was impossible for air as such to reach the heart; he considered that the pulmonary arteries received "the freshness of the air" from the bronchi. He made detailed studies, both anatomical and physiological, of the muscular system. To study the movements produced by contracting muscles, he pulled on the tendons as Galen had done, but for the purposes of illustration he joined the origins and insertions of muscles by strings along their central lines. In general he believed that, when a muscle contracted, its opponent relaxed, and this rule, together with his observation that muscles lengthened at death, seem to show that he, like Galen, recognized a muscle tone. He saw that a frog without head, heart, viscera or skin could react to stimuli, but ceased to do when the spinal cord was destroyed. He was interested in the special senses and in particular in vision. Galen had regarded the lens as the seat of vision; da Vinci decided in favour of the optic nerve on account of the inversion of the image. He noted that the pupil contracted on exposure to light, especially in nocturnal animals; he regarded the dis-

tinctness of a seen object as dependent upon the intensity of its illumination and the size of the pupil, so that it is more clearly visible with binocular vision. Finally, he had at least some idea of stereoscopic vision. In regard to the blood vessels, he regarded the heart as the origin of both veins and arteries; in this he followed Aristotle, for Galen called the liver the origin of the veins. He was extremely interested in the heart and cardiac valves, but he did not free himself from Galen's view of the passage of blood through the interventricular septum. He studied the cardiac movements in the intact animal by an ingenious mechanical device. Finally, he regarded the heart as muscular; in so doing he was less precise than Galen, who wrote that the heart is composed of a special kind of muscular fibres, which are not dependent on nerves. When we consider the work that Leonardo da Vinci did in other fields as artist, inventor, and so forth, and the degree of excellence which he attained in all of them, we may well be astounded at his discoveries in medical science.

CHAPTER IV

JEAN FERNEL (1497—1558)*

THIS chapter is introduced largely to show how a leading physician, imbued with the humanist scholarship of the renaissance but lacking the experimental method (except in so far as the thoughtful treatment of patients can be included in the term), was able to advance physiology in the mid-sixteenth century.

Fernel was born in 1497 at Montdidier, moved in 1509 with his parents to Clermont in Beauvoisis, and later went to the University of Paris, of which he became in 1519 a Master of Arts. The renaissance spirit was already enlivening letters, painting, architecture and the like, but had not yet seriously affected the University. Realizing what he had in consequence lost ("all he had done so far . . . was to pick up futilities from 'barbarian' tutors"), Fernel devoted the next five years to humane letters, with as yet no particular career in mind. In 1524, however, he went sick with a quartan fever, and this experience was probably one of the things which decided him to take up medical studies; in 1530 he was licensed to practise, and became Doctor of Medicine. Mathematics and astrology were additional pursuits during the next few years, and he also began to publish books, his first purely medical treatise being *De naturali parte medicinae Libri septem*,

* The material for this chapter derives from Sir Charles Sherrington's two books, *Man on his Nature*, and *The Endeavour of Jean Fernel*, published by the Cambridge University Press.

which appeared in 1542. In 1544 it reappeared, in revised and amplified form, as the first of the three parts of his *Medicina,* and with its title changed to *Physiologia.* The other two parts were *Pathologia* and *Therapeutice*, and the latter was enlarged in the posthumous *Universa Medicina* of 1567.

"The natural part of medicine" is a title traceable to the Faculty's division of its studies into "things natural, things non-natural, and things contra-natural." The body's healthy functioning fell into the first category, and in his book Fernel set forth the theory of the healthy body and mind, as introductory to medicine. He dealt first, however, at some length with human anatomy, which is to physiology as geography is to history, i.e. it describes the theatre in which the action takes place.*

This anatomical section was devoid of illustrations, perhaps to encourage young physicians to rely on what they saw in dissections rather than on pictures. In it Fernel mentioned for the first time the central canal of the spinal cord, a feature later described by Estienne (or Stephanus) but completely overlooked by Vesalius.

The subsequent section on physiology was little influenced by this anatomical prelude, and Fernel stated that one passed from what one could see and feel to what was known only by meditation. The divisions of the Physiology dealt respectively with the Elements, the Temperaments, the Spirits, the Innate Heat, the Faculties, the Humours, and the Procreation of Man; the functions mentioned were natural, vital, and psychic. Obviously, without chemistry and microscopy, Fernel was in considerable difficulty with his subject, but he

* Cf. Claude Bernard's dictum that anatomy serves to localize physiology.

did at least produce the second separate treatise on physiology (the first being Galen's *De usu partium*), and clarify and systematize existing ideas of the science of which, in his view, Aristotle had been the founder. He also introduced some original views. For instance, he noted that the heart was in systole when the arteries were in diastole, and vice versa. He also wrote that the blood in the body remains unclotted, not because it is there kept warm (Aristotle's view), but because the veins exercise a restraining influence upon the coagulation process. He also stated that some muscular movements occur quite apart from appetition or will.

It was, however, in his *Therapeutice* that Fernel made his major contribution to our subject. For he opened the work with a notable preface in which he enounced his view of the relation of medicine to nature. Nature's laws are inviolable, they obtain even within the body of man, and medicine comes under the dispensation of nature. As Sherrington states, "It is Fernel's merit to take up this position in the mid-sixteenth century, a time when our own Linacre, the foremost humanist physician of his time, subscribed to magical treatment by sending twenty finger-rings, blessed by the King, to Paris as cures for rheumatism."

In sum, then, we may judge that Fernel contributed all that a leading and thoughtful physician of his period could contribute to the embryonic science of physiology. But the medicine of the day was itself too full of unsolved problems for this approach to shed much light on the body's normal functioning, and the effective line of advance proved to be an entirely different one, as we shall see. Fernel's *Physiologia*, it is true, went into many editions and survived, by very many

years, its author. Boerhaave's comment on it, however, that nothing prior to Harvey was (at the time of the comment) of any use, puts it in its correct place in this history. "Natural science", according to Sherrington, "... values confirmation of experiences ... by repetition under like conditions; also it asks for quantitative measurement and precision." Fernel did not offer such, but Harvey (see chapter VIII), less than a century later, did so. In consequence, Harvey succeeded where Fernel had not.

CHAPTER V

ANDREAS VESALIUS (1514—1564)

VESALIUS *(Fig. 1)* was the son of a Belgian father, but his mother was probably English. In 1533, after five years at Louvain, he went to Paris and studied anatomy there under the ardent Galenist, Jacobus Sylvius (1478—1555), and Johannes Guenther of Andernach (1487—1574). A fellow prosector of Vesalius was Michael Servetus. In 1536 Vesalius returned to Louvain, but left next year for Venice. In December he was made M.D. of Padua, and entrusted with the duty of conducting public dissections; then or soon afterwards he was appointed professor of surgery with care of anatomy. In 1538 he produced what have since become known as his *Tabulae anatomicae sex.* In 1539 one of his students, and a lodger in the same house, was Caius, later second founder and Master of Gonville and Caius College, Cambridge. In 1543 Vesalius published at Basel the book which revolutionized anatomy, *De humani corporis fabrica libri septem.* This wonderful and beautifully illustrated work was of importance to physiology in that it gave the first complete and reasonably accurate description of the whole human body. The reception given to it was, however, discouraging and, apart from publishing a second edition in 1555, Vesalius did little further. What he had done was sufficient in any case, for at the age of 28 he had swept away the anatomical authority of over a thousand years.

He also made certain more direct contributions to physiology, for in a brief chapter at the end of *De humani corporis fabrica* he gave a concise description of the technique and results of experiments on living animals. After accurate study of the anatomy of the cadaver, he wrote, one should proceed to examine the functions of organs, or to acquire data from which those functions can be deduced, in the living animal. Like da Vinci, Vesalius recognized a reciprocal action of antagonistic muscles. By tightening ligatures on nerves, he showed the dependence of the movements of skeletal muscle on nerve supply; he also repeated experiments on longitudinal and transverse section of muscles, ligation of the recurrent laryngeal nerve and the like, which had been performed earlier by Galen. By removing the nerve sheath, he demonstrated that it was through the nerve itself that a muscle was stimulated. He noted that a cut muscle retracted. By various methods he showed that the pulsation of arteries is dependent upon the heart and is not an innate quality of these vessels. He proved that dogs could survive splenectomy. He studied the respiration of the foetus when removed or left in situ after Caesarean section and removal of the membranes; for these experiments he used nearly full-term bitches or sows. In order to see the lungs in movement he removed a rib and other tissues of a dog without damage to the transparent pleura. (This technique, incidentally, has been rediscovered in the present century, and the dog is definitely the animal of choice, as its pleura is more transparent than that of other common species.) Then he punctured the pleura and observed the effects. He studied the action of the epiglottis and noted the presence of peri-

cardial fluid. Finally, by an experiment which gave him more satisfaction than any other, he demonstrated that, if the lungs of an animal were collapsed and the heart was brought almost to a standstill, successive artificial inflations of the lungs through a reed tied into the trachea would restore the activity of the heart to normal. The repetition of these experiments would form an attractive series of demonstrations in a practical physiology course to-day. It is perhaps, however, necessary to note that most animal experiments before Harvey's time were concerned with the observation of normal function rather than with an experimental questioning of nature as to function. It is difficult to draw the line in any individual case, but the experiments of Vesalius and his predecessors would be more properly called "zooscopy", or the observation of living animals, than experimental physiology in its modern sense. At the same time, such a technique does give the observer most valuable information about normal function, is an admirable corrective to ideas gathered solely from anatomical dissection, and is still a procedure of use to the physiologist. Zooscopy needs only skilful operation and accurate observation, experimental physiology needs in addition correct interpretation, and the pitfalls which beset the interpreter can be seen in the subsequent history of our science.

To return, however, to Vesalius. He contributed in yet another way, the importance of which cannot be exaggerated, to the advance of physiology. In the first edition of his book he noted that the interventricular septum abounded on both sides with pits, but that not one of these, so far as the senses could perceive, penetrated from the right to the left ventricle. He wondered

Fig. 1. Andreas Vesalius (1514—1564).

Fig. 2. Michael Servetus (1509 or 1511—1553).

therefore at the art of the Creator, who caused blood to pass through invisible pores. In the second edition Galen's authority no longer swayed him, he had become frankly sceptical, and he did not see how even the smallest particle could be transferred from the right to the left ventricle through the septum. As we have seen in chapter II, Ibn an-Nafis had reached this point and gone beyond it three centuries before Vesalius. But the former's views had not, apparently, been retained in the literature used by the medical profession, so Vesalius, in denying the possibility of a passage of blood through the interventricular septum, helped to prepare the way for Harvey.

CHAPTER VI

PUBLICATIONS BY SERVETUS (1553), COLUMBUS (1559), BOTALLUS (1564), AND CAESALPINUS (1571 AND LATER)

OTHER writers in the sixteenth century who were dissatisfied with the traditional teaching about the route taken by blood in its passage from the right to the left side of the heart were Servetus, Columbus, Botallus, and Caesalpinus. For three of these the alternative route of choice was via the artery-like vein [the pulmonary arterial system] to the lungs and via the vein-like artery [the pulmonary venous system] back to the heart; in other words, they unconsciously came to the same conclusion as Ibn an-Nafis had done three centuries earlier, and the judgment passed on his contribution (see chapter II) applies also to theirs. The fourth writer, Botallus, was misled by fortuitous post-natal persistence of the foetal foramen ovale, and considered this passage to be the regular blood route from the right to the left side of the heart. None of the four writers had any idea of a circulation of blood in our modern sense, or advanced any experimental proof of his contention.

Michael Servetus

Michael Servetus *(Fig. 2)* or Miquel Servet (1509 or 1511—1553) was probably born at Vilanova de Xixena "in the racial no-man's land between Catalonia and Aragon" (Trueta, 1946), and he became a strange mixture of religious reformer, physician and scholar. From 1535 to 1538 he was in Paris, and there came into contact with

Jacobus Sylvius, Guenther of Andernach, and Vesalius. Guenther says that, helped by Vesalius, and "after him by Michael Villanovanus, distinguished by his literary acquirements of every kind, and scarcely second to any in his knowledge of galenic doctrine", he examined the whole body and demonstrated to the students all the muscles, veins, arteries and nerves. Long afterwards, in 1553, Servetus printed privately a thousand copies of a book which he had had in manuscript for at least seven years. This work, *Christianismi Restitutio,* aroused opposition by the heretical views it contained, and its author was burned alive at the stake in Geneva. Almost all the copies of the book were destroyed and only three, one of them imperfect, are known to-day*. It is in this book that one finds, casually introduced among theological discussions, the first sixteenth century account of the pulmonary vascular system. In it Servetus stated quite clearly that blood passes from the right to the left side of the heart, not through the interventricular septum, but through the pulmonary artery and vein by a long intrapulmonary course; it gives up sooty vapours in its passage and comes out reddish in colour. That this is the way blood passes is proved by the communications between pulmonary artery and vein, and by the size of the pulmonary artery, which is far too large for the nutrition of the lungs alone. In the lungs, and not in the heart, air mixes with the blood and becomes red in colour. Servetus compared this passage from pulmonary artery to vein with that from portal vein to vena cava within the liver.

That this break with the traditional view was

* According to J. Trueta, *The Spirit of Catalonia,* 1946, pp. 144, 186, there may also be several copies among the books in the reserved department of the Vatican. See P. Gener, *Servet,* Barcelona, 1911, p. 127.

recorded in so matter-of-fact a way is at first sight very surprising, but it becomes less so when one remembers that it was merely an alternative (if more rational) view about the route taken by a small amount of blood; the main concept of the elaboration of the vital spirit from the interaction of blood and air remained unaffected, though it is of interest that Servetus changed the site of this process from the left ventricle to the lungs. What exactly induced him to think of the pulmonary vascular route we may not, at this late date, ever discover. It is, however, easy to imagine that the idea came to him during his dissecting days in Paris, for a disbelief in Galen's intraseptal pores must have been fairly widespread among those who had the opportunity and the curiosity to examine the heart itself, and who were not bound by tradition. As a stimulus to others Servetus' contribution was possibly ineffective, owing to the destruction of all but a few copies of the book. In fact, it became generally known only through Charles Bernard, a surgeon of St. Bartholomew's Hospital. Bernard brought the passage on the pulmonary system to the notice of William Wotton, who republished it in 1694 in his *Reflections upon ancient and modern learning*.

The next account of the pulmonary system, not unlike that of Servetus, was given by Matthaeus Realdus Columbus (1516—1559), and was published posthumously in his *De re anatomica*, 1559.

Matthaeus Realdus Columbus

Columbus was born at Cremona, was at Padua with Vesalius, deputized for him in 1543, and succeeded him in 1544. In 1545 he went as first professor of anatomy to Pisa, but left there in 1548 for a chair in Rome, where he

stayed until his death. Vesalius was not impressed by Columbus, and regarded him as unlettered and unscientific. Columbus plagiarized the work of Vesalius and of Ingrassias in his book, and some have suggested that he acquired his account of the pulmonary system in a similar way, for the manuscript account of Servetus went to Padua as early as 1546. Whatever the facts may be, Columbus claimed to be the first discoverer, his account did become generally accessible, and in it he included the description of the working of the cardiac, pulmonary, and aortic valves. It is of interest that he said that *almost* all believed in the passage of blood through the interventricular septum.

The third sixteenth century contribution occurred in a short work by Leonardus Botallus, who had been born in Italy in 1530 but was of French parentage, and who became Physician to Charles IX of France. The note, for it is nothing more than that, was published in Paris in 1564 after the author's *De catarrho*, and was republished in Lyons in the following year. In it Botallus claimed to show the way, till then unknown, by which blood passes to the left ventricle. He began by saying that he was led to his discovery by the discrepancy between the accounts given by Galen and by Columbus respectively*. After previously attempting without success to check these accounts, he had returned to the task and, while dissecting a calf's heart, had found a fairly large "ductus" leading directly into the left auricle from just above the coronary vein [sinus] opening. This "ductus" or "vena" could, he wrote, be

Leonardus Botallus

* Incidentally, he was incomplete in his description of Galen's ideas, and inaccurate in his statement about the findings of Columbus.

called the nutrient vessel of the arteries and of the vital spirits, because "arterial blood" [i.e. presumably, blood *for* the arteries or, in a proleptic sense, blood that was to become arterial] was carried through it into the left ventricle and thereby into all the arteries. The pathways suggested by Galen and by Columbus were not, therefore, the true ones. The one found by Botallus was fairly large and open in calves, pigs, and dogs. In man, on the other hand, it was somewhat smaller and its course was more tortuous; in addition, it was apparently guarded on both sides by valves. Hence, coagulated blood [ordinary venous blood in the right side of the heart was regarded as coagulable] was not encountered in the left ventricle of man, but was so in that of [lower] animals.

Botallus had, obviously, stumbled upon the persistence of the foramen ovale that can occur in the adult mammal, but it was left for Harvey (1628, Cap. VI, 35) to put the discovery into its right place in the scheme of things. It is strange that Botallus had no negative findings to report — an uninterrupted series of patent foramina ovalia in the species mentioned is certainly remarkable.

Andreas Caesalpinus

The fourth contribution was that of Andreas Caesalpinus (1519—1603), whom Italy has claimed as the first discoverer of the circulation, and who was at all events the first to use the word "circulation." Caesalpinus was professor of medicine at Pisa from 1567—1592, when he went to a chair in Rome and became physician to Pope Clement VIII. In his *Quaestiones peripateticae*, 1571, and other books, among much irrelevant matter, were definite statements about the pulmonary system.

He wrote that blood flows from the vena cava into the right heart, thence through the pulmonary artery and vein into the left heart, and finally through the arteries to the whole body. He observed that veins swell on the distal side of a ligature, but adduced very little further evidence and gave no real experimental confirmation of his views. Also, there seems to be no indication that he had realized, as Harvey later did, the rapidity and volume of the blood flow. He recognized anastomotic communication between arteries and veins. The evidence is in favour of his views having been the result of theorizing rather than of experiment, but they were nevertheless a remarkable addition to the literature of the time.

It seems obvious that a certain assumption must have been tacitly made, though the writer has never seen its importance emphasized, ever since Galen postulated a passage of blood from the right to the left heart. This assumption was that a certain amount of the blood reaching the tissues through the arteries was used up by the tissues. This amount would not be very great, but over a period of time would have to be approximately equal to the chyle taken in from the alimentary canal. Up to Harvey's time, therefore, there would have been the concept of a *slow* passage of blood from the venous system to the arterial. The appreciation of a pulmonary circuit merely changed the route of this blood from Galen's interventricular passage to an intra-pulmonary one, and there is no evidence that it was accompanied, before Harvey's time, by any real appreciation of the rate and volume of blood flow. If all this is true, then the so-called discovery of the pulmonary circulation was really the partial appreciation of its anatomical

pathway, and its physiological discovery, like that of the systemic circulation, was due to Harvey. Recognition of the function of the cardiac valves, which Leonardo da Vinci, Çolumbus, and Ruini (1598) showed in their writings, was similarly powerless, in absence of a proper idea of the rate and volume of the blood flow, to lead to the discovery of the circulation.*

* While this chapter was in the press, an article on "Michael Servetus and the discovery of the lesser circulation" was published by J. Trueta in the October, 1948, number of *Yale J. Biol. Med.*, *21*. It appears, also, that there *are* copies of Servetus' book in the Vatican Library. — K. J. F.

CHAPTER VII

THE VALVES OF VEINS

MORE or less contemporaneously with knowledge of the pulmonary circuit, information was being accumulated about the venous valves. Canano (1515—1578), in 1546, told Vesalius of his discovery of valves in the openings of the azygos and renal veins, and of the veins overlying the upper part of the sacrum. These findings were not, however, published until 1564. In 1555, in a posthumous work of Jacobus Sylvius (1478—1555), membranous projections were noted as occurring in the mouth of the azygos vein, and often in those of other large veins, such as the jugular, brachial and crural veins. By 1564, then, some slight mention of these structures was available in a mass of general literature, and there were alive a number of anatomists who had actually seen them. One cannot, however, say that they were adequately recognized, and it remained for Hieronymus Fabricius ab Aquapendente (1533?—1619) to ensure this. Fabricius *(Fig. 3)* studied in Padua under Fallopius (1523—1562), and in 1565 succeeded him in the chair of surgery with care of anatomy. He retired in 1613 after fifty years of teaching, during which he had made Padua the medical centre of the world. In the sixteenth century the number of medical students inscribed there was about ten thousand, and through his pupils Fabricius influenced the subsequent course of English, German and Polish medicine. Though he

contributed more to anatomy than to physiology, and in regard to the latter adhered overmuch to Galen's views, his influence upon William Harvey gives him a definite place in the history of physiology, and Harvey's discovery of the circulation and his work on embryology were both outcomes of the years he spent at Padua. Fabricius first saw valves in veins in 1574, and he considered himself their first discoverer. In 1578 or 1579 he began to demonstrate them. William Harvey was at Padua from 1600 to 1602, and in 1603 Fabricius finally published his work, *De venarum ostiolis*, in which he described and illustrated the venous valves of man. True to Galen, using many of his ideas and even in places his actual words, he altered even the anatomical facts in some cases to fit his discovery into a galenic physiology. He thus missed the glory which might have been his, but which was to be Harvey's. For when Boyle asked Harvey, late in the latter's life, what first induced him to think of a circulation of the blood, Harvey replied that a consideration of the disposition of the venous valves made him believe that the blood must flow from the arteries to the veins. We have seen in the last chapter that the essential extra factor which Harvey supplied, and which gave life to all the scattered anatomical data already available, was his realization of the amount and rapidity of the blood flow. Caesalpinus had observed veins swell up on the distal side of a ligature, Fabricius had pictured the veins and valves in the human arm compressed by a ligature. By compressing an arm vein a little below a valve, clearing it of blood up to the valve, and then releasing the pressure, Harvey saw the direction of the circulation and obtained an idea of the rapidity of the

Fig. 3. Hieronymus Fabricius ab Aquapendente (1533?—1619)

Fig. 4. William Harvey (1578—1657).

blood flow; by successive repetitions of the same procedure, aided by arithmetical calculation, he found that more blood passed through the vein in a given time than could be accounted for without a circulation. It is of interest that the first figure of the arm in Harvey's book, Frankfurt, 1628, may have been copied from the Frankfurt, 1624, edition of *De venarum ostiolis;* there is even a suggestion in the technique of the engraving that the same hand engraved both plates (Payne: *Harveian Oration,* 1897).

CHAPTER VIII

WILLIAM HARVEY (1578—1657); LAST OF THE ANCIENTS, FIRST OF THE MODERNS, AND THE REAL FOUNDER OF EXPERIMENTAL PHYSIOLOGY

WILLIAM HARVEY *(Fig. 4)* was born on 1 April, 1578, at Folkestone, and in 1588, the year of the sailing of the Spanish Armada, he entered King's School, Canterbury. Of this period of his life there is little knowledge, but it is probable that he busied himself with natural history, for natural historians of his ability are usually born, not made. On the last day of May, 1593, he was admitted a lesser pensioner at the scholars' table at Caius College, Cambridge, and the nature of the scholarship which took him there indicates that he had probably already decided to be a physician. It was founded in 1571 by the Archbishop of Canterbury, who was a friend of Caius (1510—1573); by its regulations the holder had first to study subjects pertinent or serviceable to medicine, and then medicine itself. In 1597 Harvey graduated B.A., but from 1596—1600 he was absent a great deal from Cambridge, possibly through gout. In 1600, the year in which Fabricius published his work on embryology, Harvey went to Padua, and on St. Thomas' Day was enrolled among the pupils of Fabricius. In 1594 the latter had had built at Padua the first permanent anatomical theatre, which one can still see to-day, and in the same year Galileo Galilei (1564—1642) had commenced work in the same build-

ing which housed the theatre. Harvey had, therefore, ideal opportunities for the development of his genius. Fabricius was beginning at this time to summarize in elaborately produced and illustrated books the result of long years of careful observation of human and comparative anatomy. Galileo was there to suggest to a receptive mind the application of other sciences to the study of function. Harvey stayed at Padua until 1602; on April 25 he graduated M.D. with the greatest distinction. In this very year Fabricius must have been preparing for press his work on the venous valves.

Harvey returned to England, incorporated as M.D. at Cambridge, and settled down in London. In 1607 he was admitted Fellow of the College of Physicians, and in 1609 was appointed Physician to St. Bartholomew's Hospital. It is probable that he had been working out his ideas on the circulation, and that he gradually acquired a reputation as an anatomist, for in 1615 he was appointed Lumleian lecturer of the College of Physicians. As such, on 17 April, 1616, he lectured on the thorax, and his notes for this lecture contain his first statements on the circulation, the greatest discovery in the history of our science. "It is plain from the structure of the heart that the blood is passed continuously through the lungs to the aorta as by two clacks of a water bellows to raise water. It is shown by the application of a ligature that the passage of the blood is from the arteries into the veins. Whence it follows that the movement of the blood is constantly in a circle, and is brought about by the beat of the heart. It is a question, therefore, whether this is for the sake of nourishment or rather for the preservation of the blood and the limbs by the communication of heat, the

blood cooled by warming the limbs being in turn warmed by the heart."

From 1616 Harvey went on demonstrating the circulation and refuting the arguments of his opponents, and finally, in 1628, he published at Frankfurt his short monograph on the movement of the heart and blood in animals. It is of interest to examine the qualities which fitted him for his great achievement. To begin with, he was a born naturalist. He also had an intimate knowledge of the work of most of his predecessors: "Foremost of all among the ancients I follow Aristotle, among the moderns Fabricius of Aquapendente: the former as my leader, the latter as my informant of the way." Yet he examined their statements with care, and ascertained for himself the truth of the anatomical facts both in man and also in as many other animals — eighty species are mentioned in his lecture notes — as he could obtain. In regard to his predecessors, he makes a note "not to praise or dispraise other anatomists, for all did well, and there was some excuse even for those who are in error". Finally, having obtained an hypothesis from his study of anatomy, he devised experiments to test and verify it in living animals, and brought arithmetical calculations into his service. Because of all this we regard him as the pioneer of modern physiology — "that science which is above all others experimental". Like his master, Fabricius, he was content to wait many years before committing his ideas to print. Unlike many discoverers, he saw his own doctrine established in his lifetime.

Harvey says that, when he first set out to discover the movements and functions of the heart from actual inspection, and not from the writings of others, he

found the task so truly arduous, so full of difficulties, that he was almost tempted to think, with Fracastorius, that the motion of the heart was to be comprehended by God alone. He did, however, succeed despite all difficulties, and despite the fact that the lenses he had were insufficient to demonstrate the capillaries connecting the arteries and veins, so that he had to postulate a connection he could not see. He showed that the blood must move in a circle, that the muscular contractions of the heart are the propulsive mechanism which ensures this circulation, and that the pulsation of the arteries is dependent upon the heart. He was not content with one method of proof, or with results derived from only a few species, but drew upon vast stores of experimental and clinical facts, and used quantitative calculations to hammer home his conclusions, so that any criticism of his main contentions should be impotent and sterile. It is true that there was opposition to his views, and that in consequence his practice declined, but on the whole they were accepted much more readily than the long subservience to authority would have led one to expect. This was a great tribute to the value of the experimental demonstration of physiological facts. Yet even Harvey was wrong in other matters, and thought that the function of respiration was the cooling of the blood; it was also left to others to explain the difference between arterial and venous blood.

In 1618 he became Physician Extraordinary to James I, and in 1631 Physician in Ordinary to Charles I. From 1631 to 1646, when Charles surrendered at Oxford to the Parliamentary forces, Harvey was almost continually in close association with the King.

It is due to this that many of Harvey's notes were lost, for his lodgings in Whitehall were ransacked during his absence in 1642. It is impossible, therefore, to speak of all Harvey's discoveries in medical science, but of his work on generation, which survives, it is pertinent to say a few words.

Harvey retired after 1646, and was visited about Christmas, 1650, by his friend, Dr. Ent. To him Harvey showed his work on the generation of animals, and Ent was so impressed by its wealth of information that he persuaded Harvey to let him take away the manuscript, and in 1651 it was published. The work is in one way more interesting than the earlier book on the circulation, for it reveals more about Harvey himself. The observations contained within it are limited, as was inevitable, by the lack of adequate microscopical apparatus, but it is remarkable how far Harvey was able to progress with the help of the simple lenses which he had at his disposal. On the title page of the book Jupiter is portrayed holding in his hand an egg, from which emerge all sorts of animals from a child to insects. On the egg is written *Ex ovo omnia,* a prophetic phrase, for Harvey cannot have foreseen its widespread implications.

It is interesting to see the development in Harvey's work of the two publications for which, according to an early couplet, Fabricius was most celebrated, *The Valves of Veins* and *The Formation of the Foetus.* So true is it that in physiology progress is normally made by a more correct interpretation of the ideas of our predecessors, and that advances come slowly as the result of persistent effort rather than by spectacular leaps. As Harvey himself quoted, "Dii laboribus omnia

vendunt" (Hard toil is the price of every achievement).

Some few words may be added to complete the picture of the man to whom physiology owes so much. Harvey was an affectionate son and brother, a loyal colleague, and a generous benefactor of the College of Physicians. Though so long at Court, he was undazzled by its glamour and would pursue his researches under the most distracting conditions. Charles I was to Harvey much rather a friend interested in his experiments than a monarch involved in political difficulties, and, throughout the turbulent times in which part of his life was cast, Harvey preserved a power of detachment and concentration which is part of the make-up of a great scientist, but which must have seemed strange to his contemporaries. Time has fully justified Harvey's sense of values, and one may readily believe that the presence at Court of one so cut off from ordinary ambition and pursuits brought mental relaxation to a much harassed King.

CHAPTER IX

THE SEVENTEENTH CENTURY

"Quae in natura fundata sunt, crescunt et augentur: quae autem in opinione, variantur, non augentur." — BACON, *Novum organon*, 1620.

WITH the seventeenth century one feels that one has stepped from the ancient into the modern world. Harvey gave us one way of arriving at physiological truth, namely, the testing of hypotheses, deduced from the study of structure, by experiments upon living animals. In so doing he dealt a mortal blow to the spirits, though it must be admitted that they were long in dying. His method was used with success by other physiologists, but they were also quick to appreciate the advantages offered by the new sciences of mathematics, physics and chemistry. Mathematics and physics owed much to the pioneer studies of Galileo Galilei (1564—1642); chemistry, in relation to medicine, had its origin in the work of Valentine, Paracelsus (1493—1541), and van Helmont (1577—1644). Both chemistry and physics were advanced very much by Robert Boyle (1627—1691), who settled in Oxford in 1654, and carried out there some of the work "which made him perhaps the greatest figure in the scientific world of his time". Boyle's law was enunciated in 1662; one of the

The introduction of physics and chemistry into physiological research

portraits of him is reproduced as *Figure 5* of this book. The wise use of physics and chemistry in the seventeenth century led to progress in physiology, but overemphasis of the separate sciences as means of elucidating physiological problems had a harmful effect, in that it led to a partial division of physiologists into an iatro-physical (or iatro-mathematical) and an iatro-chemical school.

Other influences upon physiological progress

Other influences which affected the growth of physiology were the improvement of the microscope and other instruments, the foundation of learned societies in various countries, the first publication of scientific journals, and advances in knowledge of macroscopic and microscopic anatomy. The word "microscope" originated with the *Accademia dei Lincei* (see below) and was used in a letter written by Giovanni Febri in 1625. The instrument itself was evolved by the efforts of many workers, Galileo Galilei, Johannes Kepler (1571—1630), Christiaan Huygens (1629—1695), and others. In the sevententh century it was greatly improved, and its use led to important discoveries by the classical microscopists, Hooke (1635—1703), Grew (1641—1712), Leeuwenhoek (1632—1723), Swammerdam (1637—1680), and Malpighi (1628—1694). The foundation of learned societies in this century began, in its first decade, with that of the *Accademia dei Lincei,* and proceeded with the formation of those which later became, respectively, the *Royal Society* and the *Académie Royale des Sciences.* The former received its charter in 1662; the latter was originally founded, by the King's orders, in 1666, but was reconstituted in 1699 on a more formal basis to

ensure its permanence and to increase its usefulness. The *Kaiserliche Leopoldinische Akademie der Naturforscher* and the *Königliche Akademie der Wissenschaften*, to name two others, originated in 1677 and 1700 respectively (Garrison). The *Journal des Sçavans*, which began in 1665, was the first scientific journal, but it was soon followed in the same year by *Philosophical Transactions.* The importance to physiology of scientific societies and journals cannot be over-emphasized, as a perusal of the early volumes of this latter journal shows. Finally, anatomical advances of great importance to physiology were made possible by the use of the microscope and by further careful macroscopic work.

The cardiovascular system

It will be remembered that Harvey had to postulate a connection between the arteries and veins. Henry Power (1623—1668), an English microscopist, wrote in 1649 of "the minute and capillary channels" between arteries and veins, but we do not know if he actually saw them. The final proof of Harvey's theory was thus provided by Malpighi *(Fig. 6)*, who described the capillaries in the frog's lungs in 1661. As Fraser Harris put it, "Harvey made the capillaries a logical necessity, Malpighi made them a histological fact". Malpighi's work was confirmed and extended by Leeuwenhoek of Delft in a letter which he sent to the Royal Society on September 7, 1688. Leeuwenhoek *(Fig. 7)* gave a long account of the capillaries in different sites and in a large number of animals, and the scope and thoroughness of his work brought about a general acceptance of the presence of capillaries in all tissues. It thus established the circulatory system as a closed one, and gave

Fig. 5. Robert Boyle (1627—1691).

Fig. 6. Marcello Malpighi (1628—1694).

Fig. 7. Antony van Leeuwenhoek (1632—1723).

an impetus to the study of the interactions of blood and tissues. Richard Lower (1631—1691) published in 1669 a remarkable treatise on the heart, which added much of importance to Harvey's account. It gave a modern description of the arrangement of the muscular layers of the heart, definite proof of the myogenic nature of the heart beat, and an estimation of the heart's output and of the rapidity of the blood flow. Lower narrowly missed anticipating the Webers' discovery of vagal inhibition. He was the real inventor of transfusion, the technique of which he first demonstrated successfully in dogs early in 1666.

The blood

Harvey regarded the blood as a "living element of the body . . . the first to live, the last to die". The humoral doctrines probably made the blood chemistry initially more attractive than the blood histology, and existing knowledge of the former was summarized, in 1684, in Boyle's book *On the Natural History of Humane Blood*. The red blood corpuscles were first seen by the gifted but eccentric Jan Swammerdam in 1658; his account of them, however, in his great *Bybel der Natuur* (1669), did not attract attention until the Latin translation of the book, with a preface by Boerhaave, was published in 1738. In 1665 Malpighi noted the corpuscles, but did not realize their importance; he described them as fat globules looking like a rosary of red coral in the sanguineous fluid. So it was not until 1674 that their real discovery took place. In this year Leeuwenhoek gave an account of the red blood corpuscles in man and a surprisingly good measurement (7.5 μ in our equivalent) of their diameter. He followed it up by similar studies in other species, and stated that the

corpuscles were circular in mammals, but oval in birds, frogs and fishes. He also ascribed the red colour of the blood to the presence of these elements. Bidloo, in 1685, styled them "vesicles".

The lymphatic system

The lacteals and lymphatic system were also discovered in this century. On July 23, 1622, Gasparo Aselli (1581—1626) saw the lacteals by chance during an experiment; he followed up this observation by further work and in a posthumous account, published in 1627, he stated that they contained milky or creamy fluid and were provided with valves. He thought, however, that they led to the liver. Incidentally, this book contains the first *coloured* anatomical illustrations of importance. In 1651 Jean Pecquet (1622—1674) published his discovery of the thoracic duct and the receptaculum chyli; he also showed that Aselli's lacteals open into the duct and the duct itself into the venous system. Van Horne, who had been working independently of Pecquet, corroborated his findings in 1652. Harvey wrote a letter to Morison in Paris in this year, and said that he could not, on experimental grounds, accept the lacteals as the sole agents in intestinal absorption; the mesenteric veins should also be considered. Joyliffe, in a thesis for the Cambridge M.D. in the same year, gave the first account of the lymphatics, but it did not get into print. It was followed in 1653 by the publications of Olaus Rudbeck (1603—1702) of Upsala and Thomas Bartholin (1616—1680) of Copenhagen. An account of the passage of the chyle into the blood, illustrated by very ingenious experiments, is to be found in Lower's book (1669), and he finishes by saying, "The cause of our life consists in this alone, that

the blood in its continuous passage through the whole of the body carries round heat and nutriment to all the organs, and that ever-fresh chyle passes into the blood in due measure and amount, restoring with equivalent supplies the daily loss of blood-fluid and refreshing it with its continuous inflow."

Respiration

The study of respiration was greatly advanced by a group of Oxford workers, though it was Malpighi (1661) who showed that the bronchi terminate in minute air spaces in close relation to the lung capillaries. Robert Boyle, in 1660, made the first contribution by showing that a partial vacuum extinguishes life at the same time as it puts out a burning candle. The next step was taken by Robert Hooke in 1667. Hooke proved that respiration is not dependent upon lung movement, but upon the passage of air through the lungs. He showed that normally the lungs expand through the movements of the chest wall, but that an animal can be kept alive by periodic inflation of its lungs with a pair of bellows tied into the trachea. He then went farther (than da Vinci and Vesalius had done), and showed that the animal could live equally well if the lung surface was pricked with a knife to give egress to air, and a continuous current of air was passed through the partially inflated but stationary lungs. Hooke himself pointed out that "it was not the subsiding or the movelessness of the lungs that was the immediate cause of death, or the stopping of the circulation of the blood through the lungs, but the *want* of a sufficient *supply of fresh air*". In 1669 Lower described the experiments by means of which he proved that air mixes with the blood in the lungs to give the latter its red colour, while venous blood owes

its dark colour to loss of air. In 1668 John Mayow (1641—1679) published his *Tractatus duo* and in 1674 his *Tractatus quinque*, in virtue of which he was long acclaimed as the virtual discoverer of oxygen and of its importance in respiration. Professor T. S. Patterson, however, showed in a scholarly analysis (*Isis*, 1931) that all of Mayow's important concepts could be found in previously published works of Robert Boyle. The evidence was quite sufficient to depose Mayow from the false position which he had so long occupied in the history of respiration, but one must pay a tribute to his power of synthesis and attractive presentation of the knowledge that was available. Boyle, incidentally, was the first to extract blood gases; this he did in 1670 by exposing blood, and blood vessels containing blood, to a partial vacuum, but he carried this work no farther.

The pioneer of modern metabolic studies was Sanctorius (1561—1636) of Padua, who published the results of his work, without experimental protocols, in 1614.

Metabolism

Sanctorius sat in a chair suspended from a large steelyard and weighed himself at various times, such as before and after meals. His findings in the main emphasize the loss of weight due to insensible perspiration. Willis noted the sweet taste of diabetic urine in 1679, and Dekker found albumen in urine after boiling in 1694. Woodall, in *The Surgeon's Mate*, 1617, advocated limes and lemons as preventives of scurvy.

The publications about glands during the period under review form a remarkable contribution to anatomical and physiological knowledge and theory. They

Glands

begin with the discovery of the pancreatic duct by Georg Wirsung of Padua.

He had known of it for some years before he wrote about it to Riolan in 1643. It was present in man and in all the other animals which he examined, and he saw its ramifications within the pancreas as well as its entry into the duodenum. He noted that the fluid with which it was filled stained silver as bile did, but he never followed up his discovery by further work. In 1654 Francis Glisson (1597—1677) published his book on the liver. He did not, apparently, use a microscope, but he described the capsule of the liver for the first time and gave a careful account of the distribution of its vessels. Two years afterwards Thomas Wharton (1614—1673) issued his work on glands, in which he described the duct of the submaxillary gland; this had, however, been seen over a century before by Achillini (1463—1512). Wharton thought that the saliva was secreted from the blood and succus nerveus. In 1662 Stensen (1638—1686) published his description of the parotid duct, and Bellini, aged eighteen, announced his discovery of the uriniferous tubules and suggested their function. Reinier de Graaf (1641—1673), who was responsible for introducing Leeuwenhoek to the Royal Society, was almost as precocious as Bellini, and in 1664 gave an account of his studies of the pancreatic juice, which he had obtained through a quill inserted into the duct.

It was Marcello Malpighi, however, who made the greatest contribution by his work on the structure of the glands, which was published in 1666. His statements about the liver, kidney and spleen were fundamental, and little of importance was added to them for a century or more. Apart from giving details of structure, he proved that the liver is a gland for the secretion

of bile. He demonstrated the corpuscular elements in the renal cortex, greatly extended Bellini's observations on the tubules, and described the capsule, trabeculae, blood vessels and nerves of the spleen. He thought that the spleen was a contractile vascular organ, though he recognized the possibility of peculiar changes taking place in the spleen pulp, and he also described the small white bodies, attached to vessels, which now bear his name. In 1671 de Graaf stated that the pancreatic juice is one of the fundamental digestive secretions. In 1677 Peyer (1653—1712) described the lymphoid follicles of the small intestine; in 1682 Brunner gave an account of his extirpation of the pancreas in dogs (it was probably incomplete), and five years later described the duodenal glands which now bear his name. Finally, in 1695 Grew made the first observations on gastric glands.

Digestion

Ideas as to the nature of digestion are found in the posthumous work of van Helmont, which appeared in 1648, and which marks the introduction of chemical ideas into physiology. In it is contained, among certain mystical concepts, the idea that all physiological processes are due to the action of ferments. In particular, gastric digestion is said to be due to a ferment aided by an acid, though one must not assume that van Helmont meant all that we should by such a description. The first use of the word "gas" occurs in this book, and "gas sylvestre" (carbon dioxide) is described as arising during the fermentation of wine. In 1663 Franciscus Sylvius (1614—1672), the successor of van Helmont and leader of the iatro-chemists, issued a book in which he emphasized the importance of chemical concepts in

physiology. Sylvius had studied salts a great deal, and his more advanced chemical knowledge led him to omit the mysticism which had made such an appeal to van Helmont. In 1679, in a posthumous work, he stated that digestion is a process of fermentation in which the saliva and pancreatic juice play the chief parts. Sylvius was not a great discoverer, but he was a very good teacher, and to this fact he owed his influence on the thought of his time. The posthumous work of Borelli, the leader of the iatro-mathematical school, which appeared in 1680, gave another interpretation of the digestive process, for Borelli and his followers regarded digestion as the result of a mechanical trituration of the food within the stomach. Stahl (1660—1734) in 1684 reiterated the views of Sylvius.

Spontaneous generation

The theory of spontaneous generation, which had persisted since Aristotle's time, received attention of various kind during the century. Giuseppe Aromatari (1586—1660) in 1625 opposed it, and insisted that all plants grow from seeds, and all animals from the egg. This was supported by Harvey's work on the generation of animals (1651). Redi, in 1668, took the first step in the scientific refutation of the idea of spontaneous generation by proving experimentally that live ova must be present if dead flesh is to engender worms. From this time onwards it was generally accepted that readily visible organisms are not propagated spontaneously. Leeuwenhoek, in 1683, thought that micro-organisms do arise in this way and, as we shall see, this view was not finally refuted until Pasteur's time.

In 1657 Auber discovered the true nature of the testicle, in 1668 Reinier de Graaf wrote on the male

organs of generation, and in 1672 on the female ones.

Embryology, etc.

In the latter work the ovary and Graafian follicles were described, but de Graaf was at fault in his views as to the follicles. Embryology was advanced by Harvey's book in 1651, but a more modern account of the development of the chick was given by Malpighi in 1673. Malpighi was able to go beyond Aristotle, Fabricius, and Harvey because of his use of the microscope.

The nervous system

The anatomy and physiology of the nervous system showed less progress than some other divisions of the subject, partly because, as we have already said, the spirits were long in dying. René Descartes (1596—1650) was the first to suggest the reflection of nervous impulses outwards from the central nervous system. His posthumous work, *De homine*, was issued in 1662, and has been called the first monograph on physiology. This title belongs, however, to one which was published by Walter Charleton (1619—1707) three years previously. Charleton advocated the experimental method, though he was not himself an assiduous exponent of it. Descartes was a philosopher and a mathematician rather than a physiologist, and he attempted to show how the working of the human body can be explained on mechanical lines. His work is the first systematic "description of bodily responses in terms of actual — or hypothetical — neuro-muscular structures", and as such has had great influence on subsequent physiological thought. Pavlov, for instance, acknowledged Descartes' concept of the nervous reflex as the starting point of his own work on conditioned reflexes. Two years later, i.e. in 1664, Thomas Willis (1621—1675) published

his book on the brain. Lower did most of the dissections for it, and Christopher Wren the drawings: the latter is also credited with the suggestion of "the circle of Willis". The book was of importance, as the classification of the cranial nerves which it contained remained the standard for over a century. Malpighi, in 1665, demonstrated in ingenious fashion the true functions of the lingual and tactile papillae; he also differentiated the grey matter of the nervous system from the white, which he saw was fibrous. He was not sure of the function of the grey matter, but by the next year had come to the conclusion that it was glandular, one of the few mistakes which he made. Johann Bohn in 1686 discussed the reflex movements of the decapitate frog, and du Verney in 1697 successfully excised the cerebrum and cerebellum.

Muscle

The first work of importance on muscle was that of William Croone (1633—1684) in 1664. This writer pointed out that the fleshy part of muscle was the portion responsible for its contractile power, and he also attempted a geometrical analysis of muscular action. Stensen's preliminary account of his work on muscle was published in this same year; the longer one appeared three years later, and may be regarded as the beginning of modern muscular mechanics. Stensen gave microscopic details of the fibrillar structure of muscles, and recognized that the tension developed by the whole muscle is the resultant of the individual forces exerted by its fibrillar constituents. In 1669 Lower gave a number of details about skeletal muscle in his book on the heart, and in 1670 Willis and Lower independently published observations on the contractions of muscle fibres, or groups of fibres,

studied by the aid of a microscope. Lower also diagrammatically represented the wavy appearance of two contracted fibres, and proved that the contraction could occur in a denervated muscle, i.e. was independent of any inflow of spirits through nerves. Glisson buried an important observation in his book on the stomach and intestine, 1677; he showed that a limb decreases in volume, rather than increases, on contraction of its muscles; in doing so, he was one of the first to construct a plethysmograph. Previously to this, it was thought that contraction involved a swelling of muscles through inflow of psychic spirits from the nerves. The posthumous work of Borelli on the movement of animals, 1680—1, concludes the list of muscular studies of the century. It was a laborious work, but contained much that we now know to be wrong.

Two words introduced into physiology during this century were destined to become more important than their authors realized. The first was the term "cellula", which Hooke used in his *Micrographia* in 1665. The second was the term "irritability", which was employed by Glisson to express the power of living tissues to respond to stimuli of various kinds. The idea lay more or less dormant until the eighteenth century, when it was adopted by Haller and given a prominence that Glisson did not envisage when he introduced the word.

Many of the men who advanced physiology in the seventeenth century would have been outstanding figures in any age, and it is a pity that limitations of space forbid the insertion of more personal details about them. To give some idea of what this omission has cost, and incidentally to show the new scientific spirit which obtained, we may conclude with a few

sentences written about or by Leeuwenhoek, the only microscopist still engaged in active research as the seventeenth century passed into the eighteenth. For this material I am indebted to the scholarly work of Clifford Dobell. Leeuwenhoek had extraordinarily keen sight, and "insisted that he could see with the naked eye that the pulse at the wrist beat downwards rather than upwards". He never confused experimental facts with speculations. The former were introduced with the phrase "I have observed", the latter with "but I imagine" or "I figure to myself". He was never ashamed to admit a mistake which later work had proved to be such. "I have said before now that, if ever I came to err in my discoveries, I would make open-hearted confession thereof." He spoke of "an inclination I have to inquire into the beginnings of created things, in so far as 'twas ever possible for me to do so". We have mentioned only Leeuwenhoek's physiological discoveries; when we consider that he also discovered bacteria and initiated protozoology, and that all his work was done in his spare time with lenses made by himself, what praise can we deem sufficient for him? Delft was indeed a remarkable city to contain within its small circuit a scientist like Leeuwenhoek, and an artist like Vermeer.

CHAPTER X

THE EIGHTEENTH CENTURY

"But why think? Why not try the experiment?"
— JOHN HUNTER to JENNER.

TEXTBOOKS provide a fair index of the progress of a science, and at the beginning of the century one was published which remained the most popular in physiology for fifty years. This was *Institutiones medicae*, 1708, of Herman Boerhaave (1668—1738). Boerhaave was a chemist of merit as well as one of the ablest of medical teachers, and in his view all the functions and actions of the body are to be ascribed to the working of physical and chemical laws. His book was superseded by the monumental work of Albrecht von Haller (1708—1777), *Elementa physiologiae corporis humani*, 1757—1766. These volumes contain a scholarly analysis and synthesis of all previous work, and are of great value even at the present day; with them the modern systematic study of physiology may be said to have begun. Haller's own contributions to the science were more numerous than is generally supposed, and reference will be made to some of them later, but one concept which he elaborated must be mentioned here. This is his idea of "irritability". Glisson first used this term to describe his concept of an innate property of all living muscular tissue, and he regarded irritability in a more general way as the principal manifestation of life. Haller *(Fig. 8)* investigated the matter in a long series of experiments on muscle, and began to

publish his results in 1739. He found that muscle could show irritability spontaneously or, if at rest, would manifest its irritability on application of an external stimulus. Movements of cardiac and intestinal muscle were dependent solely on the inherent force within them; skeletal muscle could contract by virtue of the inherent force without nervous intervention, but it could also contract by virtue of the nervous force on stimulation of its nerves. The word "irritability" was given a less limited connotation by Johann Christian Reil (1759—1813) in 1795, and was used to denote the principal manifestation of life, or matter in motion. Reil thus reverted to the less specific concept of Glisson. The substitution of "excitable" for "irritable" may be traced to the pen of John Brown (1735—1788) in 1780.

In 1724 physiology became recognized, for the first time, as an integral part of the medical curriculum through the appointment of William Porterfield to a Chair of the Institutes of Medicine at Edinburgh. In 1758 Linnaeus (1707—1778) published the tenth edition of his *Systema naturae*, and introduced specific names for animals, though his method of classification involved certain misconceptions, as John Hunter saw. In 1796 Reil issued the first volume of the first journal of physiology, *Archiv für die Physiologie*, which thereafter had an interrupted course under various titles until 1878. The chief textbook of anatomy in the century was the *Exposition anatomique*, 1732, of Jacob Benignus Winslow (1669—1760), and of chemistry Boerhaave's *Elementa chemiae*, 1732. This latter has been described as "the most learned and luminous treatise that the world had seen on the subject".

A difficult person to place is John Hunter (1728—

1793), for many years the leading surgeon in London — difficult because, though living *in* this century, he was not particularly *of* it. For his method of attacking the problems of physiology was so peculiarly his own, and his energy in its use so great, that he rarely troubled about the work that was being done by others at home or abroad. He dissected daily from 6 to 9 a.m., and dictated notes on his dissections for some hours every night. Altogether he "anatomized" over 500 different species, many of them several times, and at his death left 13,500 anatomical specimens in his museum. He was a pioneer in geology, in fossil anatomy, and in biology. His method, as regards animal function, may be called that of comparative anatomical physiology, and it consisted in deducing the function of parts from a consideration of their anatomy in a very large number of species, though he also made many experiments and drew upon a very large store of pertinent facts derived from his surgical practice. The method is of great value when the investigator has the broad knowledge of comparative anatomy which Hunter possessed, and the deductions made by its use are at times more correct than those derived from physiological experiments made upon only a few species. Nevertheless, the deductions made solely from comparative anatomy remain nothing more than probabilities until verified by experiment, and they should always be so tested. If Hunter's work needs this criticism, modern physiology can also draw a lesson from "our John", for there is a tendency to-day to study function without a very broad basis of anatomy, and experiments are in general made upon too few species to warrant very widespread conclusions. The

John Hunter

Fig. 8. Albrecht von Haller (1708—1777).

Fig. 9. John Hunter (1728—1793).

results of Hunter's physiological work are so numerous that there is not space to include them all; there is scarcely a branch of physiology to which he did not contribute something of value, and the following accounts of progress in these branches must in most cases be assumed to require some addition from his works. His portrait is reproduced here as *Figure 9*.

The cardio-vascular system

John Floyer (1649—1734) was the first in this century to make important contributions to cardio-vascular physiology. In 1707 he published an account of the variations in pulse rate, for the accurate measurement of which he had devised a watch that ran for exactly one minute. Three years later we find him ascertaining the blood to form one-thirteenth or less of the body weight. The blood volume had been a matter of interest from Harvey's time or earlier, but Floyer's figure seems worthy of special mention. Equally quantitative in his procedure, but of far greater genius, was the Rev. Stephen Hales (1677—1761). His guiding principle may be given in his own words: "Since we are assured that the all-wise Creator has observed the most exact proportions of number, weight, and measure, in the make of all things, the most likely way to get any insight into the nature of those parts which come within our observation, must in all reason be to number, weigh and measure." The second volume of Hales' *Statical Essays*, published in 1733, contains his haemastatics, and gives records of the first measurements of blood pressure, as well as details about the variation in calibre of capillaries under different influences. The blood pressure was directly measured in horses by means of glass tubes several feet high, and the results led to

estimates of the work of the heart and more accurate ideas of the peripheral resistance. In 1736 Haller reasserted the myogenic nature of the heart beat; in 1756 he stated that the capillaries are non-contractile and his authority was such that this view persisted, despite the more accurate observations of some later workers on the subject, until 1917. Between 1756 and 1762 he published the results of some important experiments upon the venous blood flow. In these he showed that inspiration increases the inflow from the superior vena cava and decreases the inflow from the inferior vena cava, while in expiration the opposite effect is seen. In 1773 Spallanzani (1729—1799) made microscopical observations of the blood circulation in cold-blooded animals and in the embryo chick, and in 1794 Scarpa (1747—1832) gave the first proper delineation of the cardiac nerves.

The blood

John Hunter, like Harvey in the previous century, regarded the blood as a living element of the body. In 1741 Quesnay produced a classification of the blood constituents which, though elementary and imperfect, was nevertheless an advance on previous ideas and a prelude to the work of the next century. Two years later Schwencke introduced the word "haematology" in the title of his book, *Haematologia, sive Sanguinis Historia*, etc. In 1749 Senac stated that the red corpuscles were discs; he also mentioned *globules blancs du pus* (white corpuscles) as belonging to the chyle. In 1771 William Hewson (1739—1774), a distinguished pupil of William and of John Hunter, published his *Experimental Inquiry into the Properties of the Blood*. It was concerned with the process of blood coagulation, which John Hunter also

had studied with some success. Various hypotheses, unsupported by evidence of a serious nature, had been popular before Hewson's work appeared. He delayed coagulation in various ways, and succeeded in separating "coagulable lymph" (fibrinogen) from the plasma; to its formation in the plasma he thought coagulation was due. In 1773 he described the white corpuscles as derived from the lymph glands and the thymus and as passing via the thoracic duct into the blood stream; after reaching the spleen, they were, he thought, transformed into red corpuscles. He said that these latter were "as flat as a guinea". In general, however, these observations on the red cells did not gain acceptance until 1846, and most people regarded the corpuscles as being merely air bubbles.

The lymphatic system

Knowledge of the anatomy and physiology of the lymphatic system was greatly increased in the eighteenth century by William Hunter (1718—1783) and by John Hunter, but on experimental grounds they denied any absorptive power to the veins, a view which was corrected by Magendie in the early part of the next century. Hewson and Cruikshank (1745—1800) assisted them in their work, and the latter's *The Anatomy of the Absorbing Vessels of the Human Body*, 1786, is the book which marks the beginning of modern concepts of lymphatic physiology. Though these observers were wrong in denying a share of absorption to the veins, their researches, conducted upon a large number of species, put the whole matter on a much wider basis than it had previously been. The disputes, also, which their work provoked, directed attention to

the lymphatics, and this made them more generally and more rapidly recognized. Physiological knowledge is sometimes advanced in curious ways!

The cerebrospinal fluid was discovered in 1774 by Domenico Cotugno (1736—1822).

As the question of absorption has been discussed, it will be pertinent to examine next the various views which obtained about digestion. Boerhaave described

Digestion

it in his textbook as a kind of solution aided by trituration. He conceded, however, "an attenuated fermentation" in the stomach under the action of heat. It would appear that he was unwilling to reject either the iatrophysical or the iatrochemical ideas of the previous century, and contented himself with a partial synthesis of them. Haller recognized a softening effect of the gastric juice upon the food, but ascribed it to a kind of incomplete putrefaction rather than to a fermentation. He believed that bile aids the digestion of fats. René de Réaumur (1683—1757) made the first experimental advance of importance in 1752. He had a pet kite which, according to the habit of this species, would vomit after a time anything which it could not stomach. Réaumur constructed some metal tubes open at both ends, put food inside them, and gave them to the kite to swallow. When they were returned, the food inside was softened and bitter to the taste. Gastric juice obtained by putting small sponges in the tubes softened food in vitro but did not completely digest it — Réaumur had not done the experiment at body temperature. In 1772 John Hunter published his account of the digestion of the stomach after death; he saw that digestion is not dependent on any mechanical effects, but that the

stomach secretes a juice which can act upon dead, though not upon living, tissue. Stevens, in 1777, described the human counterpart to Réaumur's experiments. He had induced a stone-swallower to swallow also, and to regurgitate, little perforated silver balls containing foodstuffs; he was thus enabled to study their digestion. Spallanzani *(Fig. 10)* also was busy on comparable lines from 1776—7, but his results were not published as a whole until 1780. He greatly extended Réaumur's technique, and used it on a large number of animals, including himself. He found that trituration of the food aided digestion in certain birds, but that this trituration was effected by the gastric muscles and not by the small stones found in the gizzard. Spallanzani also performed in vitro experiments at body temperature, and demonstrated the solvent and antiseptic qualities of the gastric juice. Quantitative studies showed that digestion began after about an hour and was more or less complete within seven hours, while meat was less rapidly digested than bread or fruit. Spallanzani also worked on mammals and found that in them mastication replaced the trituration which was necessary in birds. He had an inkling of the salivary and intestinal digestive processes and came near to discovering the acidity of the gastric juice, but the chemical methods of the day were insufficient, and he concluded that the juice was neutral in reaction. As fermentation in his day was associated with the idea of effervescence, he was opposed to the view that fermentation occurs in digestion. John Hunter, in 1786, published some further observations on digestion in which, contrary to his usual rule, he gave a good history of previous work. He noted that, although the gastric

juice is frequently acid, yet on occasion, such as just before birth, an animal's stomach may contain a digestive juice without an acid reaction. Hunter in 1783 had asserted the importance of the salivary secretion, and in 1786 was of the opinion that digestion continues in the intestines. Anatomical discoveries relating to the alimentary tract include those of Vater's ampulla in 1720, and Lieberkühn's intestinal glands in 1745.

Respiration

The study of respiration at the beginning of the century was oppressed by the phlogistic theory; at the end of the century it had been relieved of this burden and had entered its modern phrase. Stahl's theory was developed from a hypothesis first put forward by Becher (1635—1681), and it was designed to explain the phenomena of combustion. All combustible materials were supposed to contain something which was called phlogiston, and burning was caused by, or resulted in the escape of, this phlogiston. The ash which remained afterwards was dephlogisticated matter. The known fact that a substance ceased to burn in a confined space was accounted for by assuming that the air had taken up from the substance as much phlogiston as it could receive. In 1754, Joseph Black (1728—1799), who made notable contributions to the physics of heat, published his *Dissertatio de humore acido de cibo orto et de magnesia*, and an English translation appeared in the following year. In this work he described the isolation, though not the chemical identification, of what we now call carbon dioxide, but what he designated in 1782 as "fixed air". By the terms of the phlogistic theory, when lime was heated, it gained phlogiston,

Fig. 11. Antoine Laurent Lavoisier (1743—1794).

Fig. 10. Lazzaro Spallanzani (1729—1799). Courtesy of the Wellcome Historical Medical Museum.

when quicklime was slaked, it lost phlogiston. Black showed that in these processes the loss and gain were actually the opposite of the theoretical. He found that fixed air could be recognized by the turbidity which it produced in a clear solution of lime water, and that it was given off by mild alkalies when treated with acid, during fermentation, and in the burning of charcoal; it was also present in expired air. It was distinct from air, though it might be in it, and was irrespirable. Antoine-Laurent Lavoisier (1743—1794) later identified it chemically, and we know now that it was the "gas sylvestre" described earlier by van Helmont. In 1766 Henry Cavendish (1731—1810) similarly isolated "factitious inflammable air" or hydrogen. Boyle had noted in 1672 that an inflammable air or gas is given off when metals are dissolved in acids, and factitious air was often mentioned in the first half of the eighteenth century. It received its present name when Cavendish determined the composition of water in 1781. Oxygen, which had nearly been recognized in the seventeenth century, was similarly isolated before it was identified, but its history is somewhat more complicated. Carl Wilhelm Scheele (1742—1786), a Swedish chemist of great distinction, probably began his work on oxygen before 1768, and had isolated the gas by the end of 1771. By 1775 he had his manuscript complete, but he did not publish until 1777. Scheele knew that his gas was odourless and tasteless, that it played an active part in maintaining combustion, was indispensable for the respiration of animals and the germination of seeds, and formed part of the air. The Englishman, Joseph Priestley (1733—1804), also isolated oxygen, and there is some evidence that he had

done so by the end of 1771, simultaneously with Scheele. We know, at all events, that on August 1, 1774, he obtained it by heating mercuric oxide by means of a burning glass. Priestley, however, could not escape from the phlogistic theory; as his gas caused an increased combustion, he imagined that it was devoid of phlogiston, and called it "dephlogisticated air". He realized that it was that part of common air which supported combustion and life. In the autumn of 1774, shortly after the experiment referred to above, Priestley visited Lavoisier *(Fig. 11)* in Paris, and at this time Lavoisier is also known to have been in correspondence with Scheele. Lavoisier was able to interpret Priestley's findings in a modern sense and his first paper, in 1775, showed that he had grasped the nature of oxidation and realized that Black's fixed air results from the oxidation of charcoal. In 1777 he suggested the name "acidifying principle" or "oxygine principle" for the new gas; in the same year he showed that in respiration oxygen is taken in by the body and carbon dioxide is given out. But here we must go back a little and discuss the isolation of nitrogen. This was announced by Daniel Rutherford (1749—1819) in 1772, though it is probable that the gas had been found earlier than this by Scheele. Rutherford did not recognize nitrogen chemically; this task was left for Cavendish, who in 1784 published his determinations of the composition of air. The rest of Lavoisier's work from 1777 to 1785 may now be rapidly summarized. He found that nitrogen made up about four-fifths of common air and was unchanged in respiration. He demonstrated that respiration is in every way analogous to combustion, that oxidation in the body results in the production of

heat, and that its products are water and carbon dioxide. He thought, erroneously, that the lungs were the site of the oxidative processes; this view he would possibly have altered, but in 1794 he fell a victim to the guillotine, and with his passing science lost one of its greatest figures. In 1789 Girtanner (1760—1800) suggested that the venous blood takes up oxygen in the lungs from the inspired air and in 1791 Lagrange, through his pupil Hassenfratz, affirmed that the dissolved oxygen of the inspired air slowly takes up carbon and hydrogen during its passage through the tissues. In 1776 Spallanzani published the results obtained by exposing animals to a limited supply of air. He concluded that cold-blooded animals were more resistant than warm-blooded and that death was the result of the action of a lethal gas, contained in the expired air, upon the nervous system. In 1778 Cruikshank showed that carbon dioxide is excreted by the skin as well as by the lungs.

The foreshadow of metabolic studies to come

Dietary treatment of scurvy was recognized when in 1747 John Huxham (1692—1768) recommended a vegetable diet for 1,200 sailors of the fleet; Captain Cook (1728—1779) also used special antiscorbutic foodstuffs during his voyage round the world, and in 1795 the Admiralty ordered a general use of lemon juice, which effectively checked the complaint. Urea was discovered by Rouelle in 1773; in 1776 uric acid was first isolated from human urine by Scheele, and in the same year T. Bergman found it in bladder stones. This year, therefore, marks the beginning of purine chemistry. The connection of uric acid and gout was shown by Wollaston, who in 1797 found the

acid in gouty concretions. In regard to animal heat, John Hunter stated that it is wrong to speak of cold-blooded and warm-blooded animals — it is more correct to differentiate animals with a permanently high temperature from those with a temperature which fluctuates with their environment. Mathew Dobson in 1776 proved that the sweetness of blood serum and urine in diabetes is due to sugar, Home and Frank formulated yeast tests for sugar in diabetic urine (1778, 1791), and the latter in 1794 defined diabetes insipidus. Cawley in 1788 described a case of diabetes in which the pancreas was atrophied. An ice calorimeter was used by Lavoisier and Laplace in 1778, and a water one by Crawford in 1788. There was thus in this century some foreshadowing of metabolic research that was to come.

The nervous system

The first publications on the nervous system which we need record were those of du Petit (1727) and of Winslow. The former disposed of the idea, current since Willis' book appeared (1664) or perhaps even earlier, that what we now call the lateral sympathetic chains had a cerebral origin. The latter introduced the idea of the sympathetic ganglia as independent centres of nervous control. Stuart's treatise on muscular structure and movement (1738) showed that the theory of reflex action had not yet been accepted in physiology, and that Galen's influence still persisted, but a remarkable change in spirit was seen in the book which Robert Whytt (1714—1766) published only thirteen years later. Whytt examined the reactions of animals after extirpation of various parts of the central nervous system, and showed that the spinal cord is essential for

reflex action. He also demonstrated that destruction of the anterior corpora quadrigemina abolishes the pupillary reaction to light — "Whytt's reflex". He applied the term "sentient principle" to that part of the central nervous system which receives sensory impressions, and localized it in the brain and spinal cord. He stated that a stimulus which was adequate for one nerve or muscle might not be so for another, and he noted that movements which originate reflexly from external stimuli are often not perceived by the individual. Haller believed that, as irritability is a specific immanent property of all muscular tissue, so is sensitivity confined to nervous tissue or to tissue supplied with nerves (1756—60). In 1751 and 1764 respectively (the first) Meckel and Johnstone added to knowledge and concepts of the sympathetic system; Johnstone's major contribution was his appreciation that the cardiac and intestinal nerves arise from the spinal marrow. In 1768 Spallanzani noted that the sexual posture of the frog is essentially a spinal reflex, and is not affected by decapitation of the animal. Cruikshank in 1776 investigated the reunion and regeneration of divided nerves, and somewhat later Soemmerring (1775—1830) gave his classification of the cranial nerves, which eventually displaced that of Willis. Prochaska (1749—1820) in 1780—84 introduced his concept of a "sensorium commune" within the central nervous system, where impressions of sensorial nerves are "reflected" upon the motor nerves, and about this time, or perhaps earlier, John Hunter anticipated Müller's doctrine of specific nerve energy, as is evidenced by the following statements. "It is more than probable that every nerve so affected as to communicate sensation, in whatever part

of the nerve the impression is made, always gives the same sensation as if affected at the common seat of the sensation of that particular nerve." "A mechanical impression on the retina produces an impression of light; a blow on the ear the sensation of sound." In 1796 Reil employed chemical agents in his investigations of the structure of nerve fibres.

The eye

The eye attracted some attention in the last decade of the century, for in 1792 Thomas Young (1773—1829) read a paper in which he showed that accommodation is effected by changes in the curvature of the lens, though he wrongly attributed this change to musculature within the lens; in 1794 Reil gave an account of the histology of the lens, and Dalton of colour-blindness; finally, in 1797 Reil figured the macula lutea.

Muscle

In regard to muscle, Baglivi's publications (1700) are the first to be considered. This observer described the gross and minute differences between striated muscle and smooth muscle, and suggested that the former kind was designed for rapid movements, the latter for long-sustained activity. It was, however, Leeuwenhoek who in 1715, at the age of 82 or 83, gave the first studied description of the microscopic structure of skeletal muscle fibres. He noted the longitudinal striations and demonstrated the existence of the sarcolemma, but he thought that the transverse striations were spiral, a view which has some adherents even to-day. In 1738 Boerhaave published the Latin version, *Biblia naturae*, of Jan Swammerdam's wonderful *Bybel der Natuur* (1669); in this book is contained the description of the first oncometers and plethysmographs, and the proof that the volume of a

muscle remains unchanged during its contraction. This proof is more satisfactory than that of Glisson, for Swammerdam used excised muscles, and the extreme ingenuity of his technique is a lasting memorial of his peculiar genius. The book itself has been described as "the finest collection of microscopical observations ever produced by one worker" (Singer). We have already noticed Haller's views on muscle, but it is worth while to add that he used a microscope to observe muscle fibres during their activity, thus following in Willis' and Lower's footsteps (1670). His experiments with nerve and muscle led to a great restriction of the doctrine of psychic spirits, though he had not the courage to dismiss them completely from physiology.

As we have reviewed the advances in neuro-muscular physiology, it will not be out of place to note here the discoveries which were made in this century about "animal electricity". John Hunter wrote about the electrical organs of certain fishes *(Torpedo, gymnotus electricus)* which he had dissected, but the real pioneer in studies of animal electricity was Luigi Galvani (1737—1798). Before 1780 Galvani had used static electrical discharges to provoke muscular contraction, but it was an experiment performed on September 20, 1786, which gave him the idea of animal electricity. Galvani had suspended some frogs' legs on copper hooks from an iron balcony, and spasms occurred every time the legs touched the iron through stimulation by the bimetal couple. Galvani, however, thought that the movements were spontaneous, and published the results of further work on the subject of animal electricity in 1791. The experiment used to be included in courses of

"Animal electricity"

practical physiology under the title of "Galvani's (first) experiment with metals". Alessandro Volta (1745—1827) pointed out that Galvani had not demonstrated animal electricity, and that his results were due to the coupling of two dissimilar metals. Galvani, therefore, set to and showed in his (second) "experiment without metals" that muscle could contract in the absence of metals, if the nerve of a nerve-muscle preparation made contact with an injured point on the muscle. This experiment was probably performed in 1793, and the result was published in 1794. The dispute between the champions of animal currents and of metal currents was terminated by the death of Galvani in 1798, and the discovery of the voltaic battery in 1799 withdrew interest from a book which von Humboldt published late in 1797. In this work, besides giving an unbiased view of the Galvani-Volta controversy, von Humboldt also described interesting experiments of his own.

Spontaneous generation

The theory of spontaneous generation received more rebuffs than support in this century. On experimental and other grounds it was opposed successively by Joblot in 1718, by Vallisneri in 1733, by Réaumur in 1738, and by Henry Baker in 1743. John Turberville Needham (1713—1781), however, in 1745 thought that his experiments proved a spontaneous generation of micro-organisms. He boiled animal and vegetable infusions in flasks and afterwards corked the flasks, but organisms were subsequently found in the infusions. Buffon (1707—1788) supported Needham's views and gave them popularity, and it was not until 1762 that the opposing faction came once more to the

attack, led this time by Charles Bonnet (1720—1793). Bonnet argued but did not prove, and it was his friend Spallanzani who finally routed Needham and Buffon by experiments which were published in 1765. Spallanzani saw that it was Needham's corking which introduced the micro-organisms; by boiling infusions for a long time and then hermetically sealing them, he demonstrated that spontaneous generation did not take place. Incidentally, his experiments explained sterilization by heat, and showed that previously sterilized organic matter could be preserved in hermetically sealed vessels. The weak point in Spallanzani's position, as Singer has pointed out, was that he sought to prove a universal negative, and this is always a difficult proposition. Hence, the idea of spontaneous generation continued to find some supporters, and persisted well into the next century.

Cowper discovered the urethral glands in 1702, and in 1778 Cruikshank investigated the passage of the impregnated ovum through the Fallopian tube. In 1780

Embryology, etc.

Spallanzani published an erroneous account of the nature of fertilization, for he supposed that the seminal fluid was the fertilizing agent, and not the spermatozoa, a mistake which was not corrected until 1825. Embryology was advanced by Caspar Friedrich Wolff (1733—94), whose *Theoria Generationis*, 1759, marks the beginning of modern embryology. In it Wolff revived Harvey's doctrine of epigenesis and opposed the then current one of preformation. More interesting is his work on the development of the chick, 1768—9, for in this he spoke of the organs being formed from "leaf-like layers", and so came very close to the concept for which von Baer

was to become famous in the next century.

Miscellaneous contributions to knowledge included Spallanzani's and Hunter's experiments on regeneration of parts of animals, Hunter's monumental work on the teeth, and his experiments on the growth of bones. In an ingenious way he proved that the growth of a bone in length is due to additions to its extremities, its growth in width to deposition on the outside and absorption from the inside.

CHAPTER XI

THE NINETEENTH CENTURY

"Quelle plus grande douceur que d'arriver chaque matin à son laboratoire, et de se dire: c'est peut-être aujourd'hui que je vais faire une grande découverte." —
CHARLES RICHET.

WITH the nineteenth century, physiological progress became so rapid that more was often accomplished in a year than had previously been done in a generation. In consequence, it is no longer possible to describe completely all the advances made in the different branches, and one must omit much that one would like to include.

One particular concept was of such general importance that an account of it must precede all else. This was what is generally known as "the cell theory". In

The "cell theory"

previous centuries, owing to the limitations of the microscope, little was known of the ultimate structure of the body. The improvement of this instrument in the first half of the century, and the invention of the microtome in the second half, led to a study of the individual cell, and to a recognition of it as the essential unit in body structure and function. The first suggestion of this coming change occurred in Oken's *Die Zeugung* in 1805, but the important dates are 1838 and 1839, when Schleiden (1804—1881) and Schwann (1810—1882) first enunciated in clear form the new ideas. Huxley in 1853 gave a fine exposition of the cell theory in all

its bearings, and in so doing provided for its general recognition in our own country. To give an account of all the individual steps would take too long, but it is to them that we owe our ideas and knowledge of protoplasm, the nucleus and nucleolus, karyokinesis, genes, etc. The work is not yet complete, but even in its early stages it had great influence on the study of embryology and, through "the neurone theory", on progress in neurophysiology, to mention but two examples.

General influences

Among other important general influences, which had effects upon physiological progress, were the discovery of the laws governing diffusion, the enunciation of the first and second laws of thermodynamics, Darwin's *Origin of Species*, Graham's investigations of osmosis and of crystalloids and colloids, and the papers of van 't Hoff and Arrhenius on osmosis and on electrolytes in solution. In 1896 Finsen founded his Light Institute in Copenhagen and began the first systematic study of the biological action of light.

Instruments and technique

Instrumental and technical advances made during the period under review include, among others, the following. Schweigger invented the first galvanometer in 1811, and Oersted's discoveries in 1821 made possible the astatic galvanometer, which Nobili produced in 1825, and which he first used for the measurement of animal electricity in 1827. In 1830 J. J. Lister, a wine merchant, read an extremely important paper on improvements which he had made in the achromatic lenses of the compound microscope, and it is to these improvements that many of the important physiological ad-

vances of the rest of the century are due. Incidentally, he has another claim to fame, for his son, Joseph Lister, was to introduce antisepsis into surgery. In 1831 Faraday discovered induced currents, and in 1845 Rynd introduced the use of the hypodermic syringe in Europe. The mercurial manometer and kymograph, for which Ludwig (1816—1895) was responsible in 1847, are described elsewhere; the introduction of anaesthetics into surgery belongs to approximately the same time, and so does the invention by du Bois-Reymond of the induction coil and the technique of faradic stimulation. Helmholtz (1821—1894) produced his ophthalmoscope in 1851, and the phakoscope and ophthalmometer in 1852. The first of these caused von Graefe to remark, "Helmholtz has revealed a new world to us". Between 1865 and 1868 Ludwig made the effective beginning of the perfusion of isolated surviving organs. Histological procedure was enormously simplified by the invention of the microtome by Wilhelm His (1866), and by its improvement in the course of the subsequent decade. Joseph Lister (1827—1912) in 1867 wrote *On the antiseptic principle in the use of surgery*, and by his work, as Moynihan has said, "has saved more lives than all the wars in all the ages have thrown away". In 1872 Lippmann invented the capillary electrometer, and in 1884 Mosso the ergograph. Rubber gloves were introduced by Halsted in 1889—90 *(Brit. med. J.*, 1933, i, 632), Röntgen discovered X-rays on 8 November 1895 and Korányi in the following year gave us the method of cryoscopy in the examination of urine. Advances in a science are largely dependent on improvements in instrumental equipment and technique, and even the incomplete list

given above shows how great was the progress in this direction.

Another index of progress is the formation of societies, the publication of important textbooks, and the foundation of journals. The following list is not an exhaustive one, but it will serve the present purpose. In 1821 Magendie (1783—1855) began the first French journal of physiology, *Journal de la physiologie expérimentale.* In 1834 *"Müller's Archiv"* commenced its course, and in the same year Müller (1801—1858) began the publication of his monumental textbook, *Handbuch der Physiologie des Menschen,* 1834—40. Henle's *Allgemeine Anatomie,* 1841, was virtually the first textbook of histology, but had not the more specific title of von Kölliker's *Mikroskopische Anatomie,* 1850—54, or of the same author's *Handbuch der Gewebelehre des Menschen,* 1852. In 1858 Brown-Séquard (1817—1894) founded his *Journal de la physiologie de l'homme et des animaux.* In 1865 Schultze issued the first number of the first journal of microscopical anatomy, *Archiv für mikroskopische Anatomie.* The same year saw the publication of Wundt's textbook of physiology. It was followed in 1866 by Huxley's textbook, which went into thirty editions. In 1868 two journals were founded: one of them, *"Pflüger's Archiv" (Archiv für die gesamte Physiologie),* is still in existence, the other, *Archives de physiologie normale et pathologique,* founded by Brown-Séquard, Charcot and Vulpian, lasted on into the nineties. Foster's textbook (1876) went into seven editions and was translated into German, Italian and Russian. Foster and Langley also issued a practical physiology

Journals, Societies, etc.

(1876). *The Physiological Society* was founded in 1876. Hoppe-Seyler (1825—1895) in the next year commenced his vast treatise on physiological chemistry, and also began to publish his *Zeitschrift für physiologische Chemie.* In 1878 the *Journal of Physiology* was founded by Foster with the financial assistance of Dew-Smith, and it was followed in the next year by *Brain.* The first International Congress of Physiologists was held at Basel in 1889 (see *Frontispiece),* Charles Richet commenced his dictionary of physiology in 1895, and the *American Journal of Physiology* first saw the light in 1898; its founder was W. T. Porter.

Physiology in Great Britain

Of special interest to British physiologists are the following details. William Sharpey (1802—1880) was the last professor (appointed, 1836) of general physiology and anatomy at University College, London, and Burdon-Sanderson, who followed him, held the first chair (1874) of physiology to be created in this country. His successors in this Jodrell professorship have been Sharpey-Schafer (1883), Starling (1899), A. V. Hill (1923), and Lovatt Evans (1926). Michael Foster (1836—1907) became professor at Cambridge in 1883; he had, however, held the post of praelector in the subject since 1870. Foster was not a great original discoverer, but he was an extremely lucid expositor of physiology and of its history, and among his pupils were Gaskell (1847—1914), Sherrington (1857—   ), Langley (1852—1925), Barcroft (1872—1947), and Dale (1875—   ). His followers as professor at Cambridge have been Langley (1903), Barcroft (1925), and Adrian (1937). The Waynflete chair at Oxford was founded in 1878, and its successive occupants have been Burdon-

Sanderson (1882), Gotch (1895), Sherrington (1913), John Mellanby (1936), and Liddell (1940). Details about other professorships are of similar interest but space is lacking, so the examples selected will have to suffice as an indication of the evolution along this particular line.

The cardio-vascular system

The neurogenic theory of the heart beat, which had been championed by Borelli in the seventeenth century, was revived by Legallois (1770—1814) in 1812, and became the generally accepted view for some decades. Laënnec's invention of the stethoscope (that "gift of science to a favoured son") in 1819 added greatly to the instrumental equipment of the physiologist. In 1825 James Black (1788—1867) published *A short enquiry into the capillary circulation of the blood,* and described contractility, though not independent contractility, of the minute vessels in the webs of frogs' and ducks' feet; his findings, pregnant as they were, failed nevertheless to achieve due recognition, for Haller's views were still dominant. In this same year E. H. Weber (1795—1878) and E. F. Weber (1806—1871) produced their important work on the hydrodynamics of wave motion, and measured the pulse velocity for the first time; by showing its slight delay in transmission, they were able to disprove the current theory, put forward earlier by Bichat, that the pulse is synchronous in all arteries. In the following year there were also two contributions of interest. Philip (1770—1851) observed central acceleration and inhibition of the heart beat as a result of stimuli applied to structures within the central nervous system, and concluded that the brain exercised a control over the heart, though he

did not discover the nervous pathways which were involved. Barry also published an account of his experiments upon the venous blood flow, and these, though not absolutely above criticism, entitle him to be called the pioneer in our ideas of a negative pressure within the thorax and of its action upon the circulation.

An advance of great importance was the invention of Poiseuille's haemodynamometer in 1828. Poiseuille (1799—1869) improved on Stephen Hales' technique for measuring blood pressure by substituting for the long glass tube a mercury manometer; this he connected to the artery by a hollow lead tip filled with an anticoagulant solution of potassium carbonate. Incidentally, Poiseuille is also responsible for many of the modern ideas of the causes of the venous blood flow. In 1831, Marshall Hall added to the influences which were adverse to James Black's views by denying the existence of capillary contractility; he was, however, the first to differentiate arterioles from capillaries on anatomical grounds. Volkmann, in 1837, observed inhibition of the heart on stimulation of the vagus, but he dismissed his result as an accidental occurrence because of his preconceived views of nerve action, for in those days the idea of nerves exerting an inhibitory effect was opposed to all accepted opinions. Purkinje (1787—1869), in 1839, described those fibres in cardiac muscle which are still known by his name. The following year was of more than usual interest, for, besides the investigations of Poiseuille on the flow in capillary tubes, there appeared almost simultaneously the abstract and concrete foundations for all later vascular research. On the one hand, Stilling introduced the term "vasomotor" as a hypothetical designation

of the nerve filaments going to supply the blood vessels, and on the other hand Henle demonstrated the presence of smooth muscle in the middle coat of the smaller arteries. The latter observer also began to investigate the innervation of the heart in the following year.

A discovery of the greatest importance to neurophysiology as well as to cardiovascular physiology was announced in 1845, when the Weber brothers demonstrated the inhibitory action of the vagus upon the heart beat. They showed it first in frogs, but later proved that it also holds good in fish, birds, and a number of mammalian species which they investigated. In the same year Claude Bernard (1813—1878), the greatest of all French physiologists *(Fig. 12)*, saw red streamlines of blood in the renal vein, though he did not publish his findings until 1858. In 1847 Carl Ludwig *(Fig. 13)*, the greatest physiological teacher of all time, added a float to Poiseuille's haemodynamometer, "had the genius to cause this float to write on a recording cylinder, and thus at one *coup* gave us the kymograph, or wave-writer, and the application of the graphic method to physiology" (Stirling). In 1847, also, von Gerlach began to inject capillaries with a carmine gelatine mixture. During the following year Ludwig discovered ganglionic cells in the interatrial septum, and Remak (1815—1865) similar cells in the sinus venosus of the frog's heart. In 1849 Schiff (1823—1896) found that stimulation of the terminal vagus fibres caused acceleration of the heart beat, and he therefore opposed the idea of the vagus as an inhibitory nerve. In 1851 Virchow demonstrated the special lymphatic sheaths surrounding the cerebral arteries, and Claude Bernard commenced his pioneer researches

Fig. 12. Claude Bernard (1813—1878).

Fig. 13. Carl Ludwig (1816—1895).

upon the vasomotor system, though his real concern at the outset was temperature and not vascular control, and it was not until the spring of 1852 that he himself began to appreciate the significance of his findings. The year 1852 is also of interest for other reasons. Bidder discovered his ganglia at the junction of the atrium and ventricle in the frog's heart, and Stannius showed that a ligature between the sinus venosus and atria will stop the heart, while, after the application of a second ligature between the atria and ventricle, the latter will recommence to beat. As the neurogenic theory of the heart beat was predominant, the resumption of the beat was supposed to be due to inhibition of Bidder and Remak's ganglia.

These discoveries were, however, of minor importance compared with others upon the effects of section and stimulation of the cervical sympathetic. Brown-Séquard, in America, showed in August of this year that galvanic stimulation of the divided sympathetic nerve results in a vascular constriction and fall of temperature on the side stimulated, and he concluded that the effect of section of the nerve is a paralytic dilatation of the vessels. Claude Bernard had already observed the vasodilatation and rise of temperature resulting from such section and he performed stimulation experiments similar to those of Brown-Séquard, but quite independently, in November, 1852. Waller and Budge confirmed the results in 1853. In 1854 Gray, and in 1855 Crisp, both suggested a reservoir function of the spleen. Other events in the latter year were von Brücke's work on the semilunar valves, Vierordt's introduction of the sphygmograph, and von Kölliker's application to the heart of the "rheoscopic

frog" effect described by Matteuci. In 1856 Schiff made experiments which foreshadowed the discovery of the vasodilator nerves; the real credit, however, for making them an accepted physiological fact belongs to Claude Bernard, who in 1858 finished his work on the circulation with the definite statement that the sympathetic is a vasoconstrictor nerve, and the chorda tympani a vasodilator one. In the same year Ludwig and Stephan investigated the lateral pressure exerted by a current of water in a tube. In 1859 Michael Foster took the first step in the disproof of the neurogenic theory of the heart beat by showing that any part of the snail's heart will continue to beat rhythmically when separated from the rest. It was nothing more than Lower had done in the seventeenth century, but it served to emphasize in the nineteenth century that the heart beat is a property of the cardiac muscle itself, and it initiated a long series of further proofs by others. In the following year Marey (1830—1904) produced his sphygmograph. During 1862 von Kölliker (1817—1905) rediscovered the branched cardiac muscle plates which Leeuwenhoek had previously described, Sucquet published the first extensive account of arteriovenous anastomoses, and von Bezold demonstrated the cardiac accelerator nerves originating from the spinal cord. In 1863—4 Goltz showed that veins respond to tapping by dilatation ("Klopfversuch"), but that they recover their tone and the circulation is restored if the spinal cord or medulla is intact. The blood flow as affected by the cord was also studied by Ludwig in 1864, and in the next year he gave an address on blood pressure; rhythmic variations of blood pressure of central origin

were also noted for the first time by Traube (1818—1876).

Ludwig and von Cyon in 1866 investigated the effect of temperature on the heart beat, and published their discovery of the depressor nerve and the nervi erigentes. Ludwig and Dogiel in 1867 invented the Stromuhr for measuring the flow of blood, and in 1868 found that the first heart sound was partly muscular in origin. Between 1869 and 1870 Lauder Brunton (1844—1916) and Schmiedeberg began to study the circulatory responses to drugs, and in the latter year Ludwig and Schmiedeberg extended Schiff's earlier work and described cardiac accelerator fibres in the vagus nerves; these were traced out by Schmiedeberg in 1871. In this same year, 1871, Bowditch (1840—1911) showed the "all or none" response and the "staircase phenomenon" of the excised heart of the frog, and Kronecker (1839—1914) proved that heart muscle cannot be tetanized. Ludwig and Dittmar, as a result of work done by them between 1871 and 1873, were the first to locate a vasomotor centre; this they found to be in the medulla oblongata. In 1872 Brown-Séquard studied the experimental production of vasomotor changes in the pulmonary circulation, in 1873 Rouget (1824—1904) wrote on the development of the contractile coat of blood vessels, and in 1875 Ludwig and von Kries made pioneer measurements of the capillary blood pressure.

The refractory phase of the heart was first observed by Kronecker and Stirling in 1874, and received its present name from Marey in 1876. A year later, Eck described his method for anastomosing the portal and inferior caval circulation, and Gaskell wrote an

important paper on the vasomotor nerves of skeletal muscle. Severini, in 1878, made the first suggestion of importance about the effects of oxygen and carbon dioxide on vascular tone when he stated that the application of oxygen caused contraction, and of carbon dioxide relaxation, of the capillaries. In the next year Rouget published his second paper, and described the contractility which capillaries possess in virtue of a network of muscular cells which ramify round them; his work, however, attracted no great attention at the time and, after Krogh's resuscitation of these "Rouget cells" in the third decade of the present century, other evidence has been produced showing that they are non-muscular and are not responsible for the changes observed in the blood flow through capillaries. In 1879, also, Burdon-Sanderson (1828—1905) and Page made the first records of the heart beat with the capillary electrometer. The isolated heart was the chief object of interest in 1880, for it was in this year that H. N. Martin (1848—1896) and Sedgwick invented a method of studying the isolated mammalian heart, and that Sydney Ringer (1835—1910) began research on saline solutions suitable for mammalian heart work. In 1881 Howell studied the cardiac acceleration produced by rise of venous pressure, von Basch produced his sphygmomanometer, and Gaskell began to study with the galvanometer the electrical conditions of the heart. Within the next three years Gompertz described the arrangement of the muscle layers of the heart, H. N. Martin studied the effects of variations of temperature and blood pressure on its beat, Gaskell and Engelmann (1843—1909) proved that the cardiac impulses are conducted by muscle and not by nerve,

and Gaskell showed that the vagus innervates cold- and warm-blooded hearts alike. In 1886 the same writer gave an account of the innervation of blood vessels, and Schrader made studies on the cardio-inhibitory centre. In 1887 Brown-Séquard found that stimulation of the cerebral cortex causes vasodilatation. In the next year Gley made valuable studies of heart muscle, and McWilliam observed the effects produced by temperature on the junction of the superior vena cava and right atrium in the mammalian heart. Waller, in 1889, made photographic records of the action currents of the living heart, and another technical advance of the year in question was the invention of Potain's air sphygmomanometer.

Nothing much thereafter needs noting until 1892; in this year Roy and Adami published a great memoir on the mammalian heart. In 1893 His showed the muscular nature of the atrio-ventricular bundle and so confirmed Gaskell's previous views on the nature of cardiac conduction; this led naturally to work on the experimental production of heart block by damage to the bundle (1895). The Riva-Rocci sphygmomanometer appeared in 1896, and in the same year Leonard Hill began his important studies of the effects of gravity on the circulation. These were to show that the mesenteric vessels are reflexly constricted whenever the force of gravity tends to reduce the cerebral blood supply. Leonard Hill produced his sphygmomanometer in 1897, and there we may leave the cardiovascular advances of the century. The number of pioneer discoveries was remarkable, and it would perhaps be unfair to distinguish any one discoverer. Lauder Brunton placed Carl Ludwig first, and there was much

to support his contention, but, if Ludwig is to be thus praised, we must also remember the Webers, Claude Bernard, Gaskell and others, who were not far behind.

The blood, cerebrospinal fluid, and lymph

Many advances were made in knowledge of the blood and its coagulation, and of the cerebrospinal fluid. In 1842 Donné discovered what he called "globulins" (i.e. what we call blood platelets) and gave their size as 1/800 mm. Like Hewson, he thought (1842—4) that the red cells were derived from the white ones. Andral, who was the first (1836) to use the term "anaemia" in its medical sense and who invented the term "hyperaemia", analysed (1843), with the help of the chemists Dumas and Gavarret, the blood's fibrin and albumen content. In 1843, also, Addison published observations on the blood corpuscles, especially the white ones, in virtue of which H. A. McCallum (1907) styled him "the world's first haematologist". In 1846 Wharton Jones divided the white blood corpuscles into granular and non-granular and described amoeboid movement. In 1848 Zimmermann gave a more detailed account of blood platelets, and in 1849 Addison described diapedesis. Vierordt (1852) produced a dilution technique for the determination of the red cell count, and gave the figure of five million cells per cu. mm. for the male human subject. The word "leucocyte" appeared for the first time in 1855 in Littré and Robin's *Dictionnaire de Médecine*. In 1863 Hoppe-Seyler produced his pioneer work on haemin, haematin and haematoporphyrin, and in 1868 showed that haemoglobin was the real colouring matter of the blood. In this same year, 1868, Neumann and Bizzozero both showed that the mature

erythrocytes were derived from nucleated red cells in the bone marrow. In 1874 Osler published further work on the blood platelets and stated that they formed the bulk of white thrombi. From 1875 on Ehrlich worked with aniline dyes as staining agents, and his success with this technique led to his publications on the specific granules of the various cells and to the formulation of his modern classification of the cells. In 1877 Hayem called the platelets the third element of the blood. Gowers, in the same year, produced not only the term "haemocytometer" but also his modification of Malassey's original (1874) apparatus; in the following year he produced his haemoglobinometer. In 1882 Bizzozero introduced the name "platelets". From 1882 onwards Metchnikoff studied the phagocytic properties of white cells, coining the actual term "phagocytosis" in 1886. In 1883 Ehrlich established the origin of the granular leucocytes in the bone marrow, and in 1890 Howell gave the life history of the blood corpuscles.

Coagulation was studied by Buchanan (1845), Schmidt, Joseph Lister (1859—63), Hammarsten (1875), Wooldridge (1883), and Almroth Wright (1891). Buchanan extracted fibrin ferment, Schmidt gave it its name, and Hammarsten showed that fibrinogen is converted into fibrin. Lister noted that coagulation of the blood within the blood vessels was dependent on their injury, and Almroth Wright was the first to point out the role of calcium salts in coagulation.

The cerebrospinal fluid was described by Magendie in 1825, but Faivre's histological studies of the structure of the choroid plexus in 1855 caused the abandonment of Magendie's view that the leptomeninges produce the fluid. The formation of lymph was attributed to

a secretory process by Heidenhain in 1880, but Starling (1866—1927) in 1896 propounded a more mechanical explanation, which has since been developed farther but has not altered in its essentials.

Respiration

Lavoisier, as we have seen, thought that oxidation occurs in the lungs. Lagrange, on the other hand, thought that it occurred in the blood. At the end of the eighteenth century, in addition, there was no idea of a metabolism delicately adjusted to the physiological requirements of the organism. In the nineteenth century, the tissues gradually became recognized as the chief seat of the oxidative processes, and before its end the confused ideas as to the regulation of respiration had begun to receive form and order in the hands of John Scott Haldane (1860—1936). Spallanzani, in a remarkable memoir published posthumously in 1803, added much to previous knowledge. By experiments made upon a large number of species of widely different habits, he established as an accepted fact the necessity of oxygen for life, and he also showed that the oxygen taken in by the respiratory organs, whether lungs, gills, trachea or skin, is carried by means of the circulation to the tissues. Further, by experiments upon snails in an oxygen-free atmosphere, he showed that evolution of carbon dioxide can occur independently of oxygen absorption. Knowledge of the nervous mechanism of respiration had its beginnings before this century, and can indeed be dated back to Galen, but it is not incorrect to give special importance to the year 1811, in which Legallois found that a lesion of a small area in the medulla oblongata causes inhibition of respiration. Many years later the respiratory centre so discovered was shown by other observers

to be bilaterally represented, since section of the brain-stem down the mid-line produced no ill effects. In 1824 Edwards extended the work which Spallanzani had done on snails, and he was able to show that frogs, fish and newborn mammals likewise continue to produce carbon dioxide when placed in an atmosphere devoid of oxygen. These experiments emphasized, though they did not prove, the idea that carbon dioxide is produced in the tissues and carried by the blood to the lungs. In 1834 Schwann showed that oxygen is necessary for the development of the embryo.

Three years after this, H. G. Magnus made the first effective attempt to analyse the amounts of the various gases in the blood, and in so doing gave the first experimental confirmation of the belief that the tissues are the seat of the oxidative processes. In 1839 Pereira wrote that "The impression produced on the pulmonary extremities of the par vagum, by the carbonic acid in the lungs, is supposed by some physiologists to be the ordinary stimulus to inspiration". Subsequent to this, various improvements were made in the methods and instruments employed for the extraction of the gases, e.g. by Ludwig and Setschenow in 1859, by Pflüger (1829—1910) in 1865, and by Leonard Hill in 1895. Magnus in his pioneer experiments extracted the gases by exhaustion, and his results showed that, while oxygen, carbon dioxide and nitrogen are present in both arterial and venous blood, oxygen is present in greater amount in arterial blood, and carbon dioxide in venous blood. It followed, therefore, that oxygen was given up to the tissues by the blood, and carbon dioxide received from the tissues by it. The method of carriage of the gases in the blood was, however, undecided. In 1845

Mayer (1814—1887) pointed out that living animals derive their kinetic energy, as well as their heat, from the potential energy of the oxidative processes. In 1847 Traube, as later also Rosenthal, described the increase in respiration rate which follows upon stimulation of the central end of the cut vagus nerve in the neck. The spectrum of haemoglobin was discovered in 1855. Two years later Lothar Meyer noted that the amount of oxygen liberated from the blood under reduced pressure did not increase in proportion to the reduction in pressure; this seemed to show that the gas was in chemical combination, and Liebig suggested that the gases were in some loose combination with an unknown substance. In 1858 Claude Bernard stated that carbon monoxide displaces oxygen from the blood, and Pettenkofer (1818—1901) introduced a method for the estimation of carbon dioxide in air and in water.

In 1862 Rosenthal produced apnoea by excessive artificial ventilation, and his results gave rise to the idea that the condition is the outcome of over-arterialization of the blood going to the respiratory centre. Hoppe-Seyler in this same year obtained crystalline haemoglobin from the red blood corpuscles and attributed oxygen-carrying power to it. Stokes made a detailed spectroscopic study of the same substance two years later and showed that oxygen can be removed from it by reducing agents. In the same year, 1864, Rosenthal had made further investigations of the action of the vagus upon respiration; he showed that section of both nerves caused a slowing and deepening of breathing without much change in the total ventilation. In the next few years Pflüger proved that the nitrogen in the blood is in simple solution, and in 1867 Zuntz

(1847—1920) made the pregnant suggestion that the carbon dioxide is carried in the plasma in virtue of some substance present in the red blood corpuscles; his ideas, however, were incorrect in their details and final proof of his theory had to wait for Hamburger and others in the present century. Traube, in this year, made an observation which attracted less attention than it should have done, for he found that apnoea can be produced by excessive ventilation with an inert gas, such as nitrogen and hydrogen, though such ventilation has to be more violent to produce the effect in the absence of oxygen. Hence Rosenthal's over-arterialization of the blood could not be merely, if at all, synonymous with increased oxygenation. In 1868 Pflüger showed that excess of carbon dioxide, if not too great, or diminution of oxygen could excite the respiratory centre. In the same year Hering (1834—1918) and Breuer demonstrated that, normally, distension of the lungs stimulates the vagal endings to end inspiration and initiate expiration, while deflation of the lungs similarly tends to end expiration and initiate inspiration. Hering styled it the self-regulation of breathing. By 1872 Pflüger had proved that practically all the oxidative processes occur in the tissues and not in the blood.

Six years later Paul Bert (1830—1886) issued his important book, *La pression barométrique*, in which he quite clearly demonstrated that it is the partial pressure of a gas in the atmosphere, and not its percentage, that is of physiological significance. He also saw that the primary cause of the effects of altitude is the low partial pressure of oxygen. His findings were, however, to be obscured by a false theory which Mosso put

forward and which remained dominant until 1917. In 1885 Miescher, in experiments on human beings, found that a small increase in the carbon dioxide percentage of the inspired air causes a considerable increase in the breathing, while a corresponding diminution in the oxygen percentage is ineffective. He concluded, therefore, that it is the carbon dioxide percentage, and not the oxygen percentage, which normally regulates the breathing. In 1888 Geppert and Zuntz investigated the effect of muscular work on respiration by tetanizing the hind limbs of animals after section of the spinal cord. They showed that the cause of the increased breathing was the altered condition of the blood, but, since the carbon dioxide in the blood was less and the oxygen greater in amount than usual, they concluded that it was neither carbon dioxide excess nor oxygen diminution that produced the effects, and suggested as a stimulus an acid substance produced within the muscles. In 1889 Head's work with a misleading technique, the diaphragm slip method, gave rise to a general belief in vagus apnoea, and this in turn became elaborated into the idea that all apnoea is vagus apnoea.

It was soon after this, at a time when conflicting views were rife as to the causation of respiration, that J. S. Haldane commenced his work on the subject, and began to analyse and to correlate the scattered results of his predecessors. In 1892 he described "a new form of apparatus for measuring the respiratory exchange of animals", and put gas analysis on an accurate basis. Then in 1893 he and Lorrain Smith published the results which they had found on rebreathing air in an air-tight respiration chamber.

These showed that a small increase in the carbon

dioxide percentage of the air is an effective stimulus to respiration, while the oxygen percentage has to drop as low as 14 per cent. before anything happens. It is of interest that this effective beginning of the modern study of respiration, as well as much of the work that followed it, was carried out with the human being as the subject. Others, as we have seen, had made experiments on themselves in previous centuries, but the workers on respiration can justly claim that they were the effective founders of the experimental physiology of man. The century closed with the publication of Mosso's "acapnia" theory of 1897, and of Haldane's *Methods of Air Analysis* in 1899. Mosso (1846—1910) had been working at a great altitude on Monte Rosa and, ignoring Paul Bert's correct deductions of 1878, he concluded that mountain sickness was primarily due to the increased washing out of carbon dioxide from the blood in the lungs. This faulty conclusion, as we have noted, was to hold up progress in the study of the effects of altitude for twenty years.

Physiological chemistry

Before 1800 a few substances of biological interest had been isolated by Scheele and others; during the nineteenth century scarcely a year passed without some important addition being made to the list. It is impossible to give all the details here, but as an example it may be stated that twelve of the amino-acids were known as constituents of protein by 1900. Liebig (1803—1873) and Wöhler (1800—1882) were two of the great chemists in the first half of the century, and Kossel and Fischer's names had come into prominence by the end of the second half. Wöhler may be said to have started modern metabolic chemistry by his discovery, in 1824,

that benzoic acid given in the food is excreted as hippuric acid in the urine. In 1828 (see McKie, *Nature*, 1944, *153*, 608) he reported that urea had been produced during his purification of the white crystalline substance resulting from the reaction between lead cyanate and liquid (i.e. aqueous) ammonia. He wrote to Berzelius about these experiments, saying that he could make urea "without kidneys or a living animal, be it man or dog, being required". For the production of the cyanate, however, organic matter had been required, and there was no *synthesis* of urea in a chemical sense, nor had the first gap been made in the wall between the organic and inorganic compounds. This idea was given publicity by Wöhler's biographer after Wöhler's death in 1882, and has been reiterated by medical historians in comparatively recent times. Analysis of the facts, however, shows that the popular story is false and that this particular ghost should be laid once and for all. In 1832 Liebig and Wöhler demonstrated that a complex organic group of atoms may form an unchanging constituent of a large series of substances, and this "organic radicle concept" has been of extreme value in all subsequent research. It is to Liebig, incidentally, that we owe chloroform (1831). If we might isolate one other discovery among so many, it would be that of phenylhydrazine by Emil Fischer (1852—1919) in the seventies, for this substance has been of such importance that Abderhalden has styled it "the pathfinder of carbohydrate chemistry". It is a cause of real regret that lack of space prevents mention of the other chemists and of their discoveries, for these advances were one of the more notable features of physiological progress in the nineteenth century.

Lavoisier initiated the modern study of metabolism, but there were some errors in his views. He thought that the carbon dioxide produced was approximately equal to the oxygen taken in, that carbon and hydrogen were the substances oxidized, and that the amount of oxidation was determined by the amount of oxygen taken in and of oxidizable stuffs presented to the organism. He knew that muscular exercise increased the intake of oxygen and output of carbon dioxide. The study of metabolism in the nineteenth century included the chemical identification of the various substances ingested and excreted by the body, and quantitative analyses, which became ever more exact, of the processes concerned in metabolism. The earlier workers in this second field were chiefly French, the later almost without exception German.

Metabolism

In 1819 Magendie showed that protein was necessary in the diet. In 1836 the word "metabolism", or, rather, its German equivalent, was used for the first time to indicate the changes occurring when foodstuffs are broken down within the body. Three years later Robiquet and Thillaye initiated the concept of a heat production proportional to surface area, while Boussingault made the first attempt to analyse and balance the ingesta and excreta; others soon followed him. In 1842 Liebig stated that it is not carbon and hydrogen that are burned in the body, but protein, carbohydrate and fat. He said that the nitrogenous bodies, urea and uric acid, found in the urine are proportional to the amount of protein destroyed in the body. The non-nitrogenous residue of the protein is oxidized to carbon dioxide and water. He believed that oxygen caused the combustion of carbohydrate and fat, but that muscular

work caused the breakdown of protein. The heat produced in oxidative processes was, in his opinion, quite adequate to account for the preservation of the body temperature despite the loss of warmth from the body. In 1845 and subsequent years Bergmann elaborated his idea of a heat production proportionate to surface area, and in 1848 Helmholtz declared that the muscles were the main source of heat.

Regnault (1810—1878) and Reiset, in 1849, devised a respiration apparatus for animals, and measured the carbon dioxide output and oxygen intake under varying conditions. They decided that heat is derived from chemical reactions, and that the oxygen present in some substances is in part responsible for the carbon dioxide output. They noted that some foodstuffs are not completely broken down. In their conclusions can be seen a precursor of the law of surface area, for they noted that the consumption of oxygen was greater per unit weight in smaller animals. In 1852 their work was followed by Bidder and Schmidt's *Die Verdauungssaefte und der Stoffwechsel* (The digestive juices and metabolism). These two workers noted that metabolism was a function of the amount of food taken in and of what they called the "typical metabolism" of the individual. The "typical metabolism" was practically identical in animals of the same body volume, surface area and temperature. Carl Voit (1831—1908), who was to become the leader in metabolic research and whose portrait is reproduced here as *Figure 14*, demonstrated in 1857 his idea of nitrogenous equilibrium and also showed that 1 g. nitrogen excreted was an index of the breakdown of 6.25 g. protein. Three years later he and Bischoff published *Die Gesetze der Ernährung des*

Fig. 14. Carl Voit (1831—1908).

Fig. 15. Ivan Petrovich Pavlov (1849—1936).

Fleischfressers (The laws of nutrition in the carnivore). In this they showed the requisites for the establishment of nitrogenous equilibrium, and noted that carbohydrate had a greater sparing action than fat upon protein metabolism. They stated their agreement with Liebig's view that oxygen caused the oxidation of carbohydrate and fat, while muscular work caused the breakdown of protein. Voit was, therefore, surprised to discover later in this same year that muscular exercise did not increase protein metabolism.

About this time Voit became desirous of making an apparatus for determining the respiratory exchanges of man. With the financial backing of the King of Bavaria and the technical assistance of Pettenkofer, he accomplished this in 1861, and thenceforward was able to measure exactly the carbon excreted in the expired air, faeces and urine. From the nitrogen excretion he could calculate the protein metabolism and so, with the other data, he was able to determine the metabolism of all three foodstuffs. In 1865 he first propounded the view that oxygen is not the cause of metabolism, but that oxidation is a sequel to the breakdown of substances by the living tissues. In other words, metabolism is determined solely by tissue needs. Between 1866 and 1873 he and Pettenkofer issued a series of classical papers on the metabolism of men and of lower animals under various conditions. In 1870 Voit stated that the rate of respiration is the result of oxidation, but not its cause. In 1877 Pflüger added confirmation of this view by showing that the oxygen consumption of a rabbit was the same during quiet breathing and during artificially produced apnoea. In 1881 Voit, in his *Physiologie des allgemeinen Stoffwechsels und der Ernährung* (Phys-

iology of general metabolism and nutrition), stated that protein is the most easily metabolized foodstuff, then carbohydrate, and lastly fat. The function of fat and of carbohydrate was to provide energy for muscular work, of protein to supply the more particular needs of the tissue cells. Protein probably provided in its breakdown material for body fat.

In 1883—84 Max Rubner (1854—1932), Voit's greatest pupil, began to make accurate measurements of the calorific value of various foodstuffs, nitrogen residues, etc., and this work led to the enunciation of the idea that carbohydrate and fat are interchangeable on the basis of their energy equivalents. Rubner gave us the heat values of protein, fat and carbohydrate, and he stated the general law that the heat production of mammals is proportional to their surface area; he was also responsible for the concept of the specific dynamic action of foodstuffs in excess, and for much in our present views of heat regulation. He viewed metabolism from the standpoint of energy, and pictured molecular cleavage producing ever fresh supplies to make up for the unpreventable loss that occurs in all living beings. In 1891 he devised an apparatus for the simultaneous measurement of the metabolism of the dog by indirect and direct calorimetry, and the result of a six weeks' experiment was a justification of the indirect process by the direct. In 1892 Atwater became desirous of making a similar apparatus for man, and this desire resulted in the production of the Atwater-Rosa calorimeter in 1897. In 1892 Pflüger showed that Voit had used wrong values in his calculations, and that protein is not the usual source of body fat; in 1895 Hirschfeld noted that the presence of carbohydrate is necessary for

the complete breakdown of the fats. A portable apparatus for measuring respiratory exchanges in man was designed by Zuntz in the latter part of the century, and was much used by Magnus-Levy in clinical cases from 1893 onwards. This account of metabolism in the nineteenth century contains no word about various subsidiary advances which could with profit be included in a longer work. It is hoped, however, that it may leave a clear impression of the main lines along which this branch of physiology progressed.

Digestion

Advances in knowledge of the physiology of digestion formed so striking a part of the general progress during the century that there is some excuse for detailing them at length. In 1803 J. R. Young (1782—1804) came to the conclusion, from experiments on many animals, and himself, that an acid is normally present in gastric juice and is responsible for its solvent power. He thought, however, that it was phosphoric acid. Incidentally, he noted that the flow of gastric juice and the flow of saliva were associated and simultaneous. In 1822 Beaumont (1785—1853), in America, began his studies on Alexis St. Martin, a trapper who developed a gastric fistula as a result of a gunshot wound in this year. Two years later Prout (1785—1850) proved that free hydrochloric acid is present in the gastric juice of various animals. His results were confirmed by Tiedemann (1781—1861) and Gmelin (1788—1853) in 1826, and they also reported a sulphocyanate in the saliva. In 1833 Beaumont published the results of his observations on Alexis St. Martin. He was the first to advance physiology by the study of a gastric fistula and he was also, in virtue of this work, the pioneer of experimental

physiology in the United States. He gave a description of the mucous membrane and of the movements of the stomach, and noted the effects of various foodstuffs upon the gastric flow. He also concluded that there was an active principle present in addition to the acid. He left two misconceptions, first, that there is no gastric secretion without food being present in the stomach and, secondly, that foods or indigestible solids cause the stomach to secrete by a mechanical action on its mucous membrane. In the following year Eberle suggested that there might be one or more ferments in the gastric secretion and he also thought that the pancreatic juice might aid the digestion of fats. In 1835—6 Schwann and Müller extracted a crude preparation of pepsin and found that it would convert albumens into peptones in vitro. Purkinje and Pappenheim also noted, in the latter year, the proteolytic power of pancreatic extracts. In 1839 Wassmann isolated an impure pepsin and stated that it was produced chiefly in the fundus. Schwann, two years after this, obtained bile by means of a biliary fistula and came to the conclusion that it was essential to digestion. Claude Bernard, writing on the gastric juice in 1843, showed that it had an action upon cane sugar, for if the sugar was injected into the blood after it had been acted upon by the juice it could no longer be recovered in the urine. In the next year, Valentin found that the juice expressed from the pancreas would cause a cleavage of starch. In 1845 Miahle prepared ptyalin.

In 1846 Claude Bernard began his great work on pancreatic secretion, and in the next few years he showed that pancreatic juice emulsifies fats and converts them into fatty acids and glycerine, that it changes

starch into sugar, and that it dissolves the protein residue which is not attacked by the gastric juice. In 1851 the innervation of the submaxillary gland was discovered in Ludwig's laboratory. As a result of Beaumont's observations various workers had been stimulated to study gastric secretion by means of experimental gastrostomies, and among these were Bidder (1810—1894) and Schmidt (1822—1894), who found by this method that the hydrochloric acid is produced by the gastric glands, and who announced the fact in 1852. They also noted that the sight of food will produce a copious flow of gastric juice. Between 1857 and 1863 Corvisart found that pancreatic juice will dissolve proteins at body temperature in media of various reactions, and that bile is not a necessary adjuvant to the process, as Claude Bernard had thought. Between 1859 and 1862 Meissner studied the action of gastric juice upon protein digestion, and stated that proteins are not completely digested in the stomach by pepsin. The first fairly pure preparation of this substance was made by von Brücke (1819—1892) in 1861, and his work was followed in the next year by Danilewski's isolation of trypsin. The sugar-digesting ferments of the salivary glands and of the pancreas were studied by Cohnheim in 1863, and four years later Schiff noted that the reflex flow of saliva from a parotid fistula in the dog varied with the methods and foodstuffs employed in stimulating the flow. In 1869 Voit stated that the hydrochloric acid in the gastric juice is derived from the chlorides of the blood plasma, a view that was corroborated by Cahn in 1886. Leube (1871) and Külz (1875) were the first to use the stomach tube to obtain

gastric juice, and they also introduced the technique of fractional analysis.

Between 1876 and 1883 Kühne (1837—1900), who gave us the terms "trypsin" and "enzyme", carried out his classical experiments on pancreatic digestion; he found that the residue of protein which is unaffected by pepsin is attacked by trypsin and gives rise to tyrosine, "leucine" (a mixture of amino-acids), and complex substances over which trypsin has no digestive power. In 1878 Heidenhain (1834—1897) described the histological changes occurring in the gastric glands during their activity. He had improved on the gastrostomies of earlier workers by his invention of the gastric pouch. Heidenhain's pouch, however, did not retain its nerve supply, and it remained for his pupil, Ivan Petrovich Pavlov (1849—1936), to correct this defect, and to begin the brilliant series of experiments which has made his name famous in the physiology of digestion. In the same year in which Heidenhain described his work, Richet provided another idea which may have influenced Pavlov, for he studied a patient who had a stricture of the oesophagus and a gastric fistula, and noted that the sight of food produced a copious flow of gastric juice. In 1879 Pavlov *(Fig. 15)* published three papers on pancreatic secretion, and in one of them he described a new method for making a pancreatic fistula. Langley followed up Heidenhain's histological observations in 1880 by intravital studies of the gastric glands during activity, and in the same year Rutherford noted that the introduction of acid into the duodenum was followed by an increased flow of bile from the common bile duct. In 1888 Pavlov showed that the vagus nerve is the secretory nerve to the pancreas, and

from 1888 to 1900 he was continuously busy with that research on digestion which laid the foundation of our modern ideas on this subject. In 1893 Bekker, a pupil of Pavlov, applied acid to the duodenal mucosa and evoked a flood of pancreatic juice. His results were confirmed by another pupil, Dolinski, in the following year, and in 1899 Pavlov himself discovered enterokinase.

Renal functions

Research on renal functions was concerned primarily with the mechanism of secretion, though Schmiedeberg in 1876 showed that hippuric acid is synthesized in the kidneys. Bowman (1816—1892), in 1842, was the first to recognize clearly the relation of the glomerulus and tubules, and he propounded the idea that water (and ? salts) pass out through the glomerulus into the tubules, where it dissolves the more or less solid substances, such as urea, which have been secreted by the tubules. Bowman's hypothesis was, however, unsupported by experiment until 1874. Two years later Ludwig put forward his physical theory that the glomerulus is a passive filter, and that the secretion of urine is primarily dependent upon the heart beat. The blood pressure causes a dilute solution of non-protein substances to escape from the blood through the glomerulus, and this solution is concentrated osmotically in the tubules by passage of fluid from it into the lymph. In 1854 Ludwig's ideas were supported by Goll, who showed that changes in blood pressure cause corresponding changes in the urinary flow, but by 1856 Ludwig had recognized that his theory was imperfect, for the substances in the urine did not bear the same proportions to each other that they did in the blood. He had thus either to give up the

idea of glomerular filtration or else to accept differential absorption in the tubules. In 1869—70 he and Ustimowitsch found that, when the blood pressure had fallen so low that secretion had ceased, injection of urea caused it to begin again. This result caused him to adapt his views, and to say that the effect of the blood pressure is modified by the chemical composition of the blood, i.e. glomerular activity is due to osmosis through a semipermeable membrane.

In 1874 Heidenhain advanced experimental evidence in support of Bowman's hypothesis, and divided physiologists into two camps. It became of paramount importance, in consequence, to discover some method of studying the function of the tubules apart from the glomeruli, and to this end Nussbaum devised his experiments in 1878. The basis of these was the idea that the glomerulus in amphibia is supplied only by the renal artery, while the tubules are supplied by the renal portal vein, so that ligation of the renal artery would isolate the tubules. Nussbaum's results supported the Bowman-Heidenhain theory, but Adami in 1885, in Heidenhain's own laboratory, found that blood could reach the frog's glomerulus by routes other than the renal artery. The whole question of the functions of the glomerulus and tubules was unsettled, therefore, at the close of the century, and the main contribution of this to the succeeding century was a clearer understanding of the specific problems which remained to be solved.

Claude Bernard's work on the liver from 1848 to 1857 led to the isolation of glycogen, and it was a consideration of the changes occurring in the blood during

Fig. 16. Edward Albert Sharpey-Schafer (1850—1935).

Internal secretions

its passage through the liver that gave him the idea of internal secretions. Incidentally, his discovery of glycogen proved that the body could anabolize as well as catabolize. Moritz Schiff had begun work on experimental thyroidectomies before the discovery of glycogen was announced, so he is also a pioneer of endocrinology, and Brown-Séquard likewise has some claim to the title, because from 1856—8 he was producing Addison's disease experimentally in animals. The first active extract of the adrenals was made by Oliver and Schäfer *(Fig. 16)* in 1894, and it produced a rise of blood pressure on being injected into the blood. The thyroid attracted a great deal of attention throughout the century. In 1822 Dumas and Coindet noted the value of iodine in the treatment of goitre, and in 1895—6 Baumann found that iodine, in fairly firm combination, is a normal constituent of the thyroid gland tissue; he isolated iodothyrin and showed the relation of the thyroid to iodine metabolism. In between these dates various treatments, such as grafting and administration of extracts, had been tried for the cure of clinical and experimental myxoedema. This condition was noted in patients as early as 1850, but it was Gull's paper in 1874 that made it generally recognized, and G. R. Murray was the first to use an extract for therapeutic purposes in human cases in 1891. The effect of thyroid disease on the metabolic rate was observed by F. Müller in 1893, and Magnus-Levy measured the variations in gaseous exchange in 1895.

Friedleben, in 1858, made the first studies of thymus functions. The parathyroids were first described by

Sandström about 1889, Gley in 1891 pointed out the danger to life if the parathyroids were removed in thyroidectomies, and von Eiselsberg in the following year showed that these glands are in some way concerned with the prevention of tetany. Wilks described acromegaly in 1869, and in 1886 Marie stated that it and gigantism were due to pituitary lesions. In 1894—5 Oliver and Schäfer prepared an active extract of pituitary, while Howell investigated the pressor action of the posterior lobe in 1898.

The internal secretion of the pancreas was shown to be of importance in connection with diabetes before the end of the century. As early as 1856 Schiff had made experiments on artificial diabetes, and in 1869 Langerhans described the islets, but it was not until 1889 that von Mering and Minkowski began to show, by experiment, the relation of pancreatectomy to diabetes. It becomes more difficult, as the years go on, to break entirely fresh ground in physiology, so the discovery of internal secretions in the nineteenth century was a very remarkable achievement, and its implications for physiology and for medicine are of the greatest import.

The nervous system

At the beginning of the century many of the essential features of reflex mechanisms were known or were discoverable in the literature, but knowledge of the minute anatomy of the nervous system was practically non-existent, the functions of the reflex were not understood, and the idea of the integrative action of the nervous system was yet to come. It was generally believed that the same nerve conducted both motor and sensory impulses. During the century two concepts in particular assisted the progress of neurophysiology, and both were

dependent on the cell theory, which in its turn was dependent on advances in histological methods. These two concepts were the neurone theory and the idea of the synapse.

The "neurone theory" and the "synapse concept"

The neurone theory was to the nervous system what the cell theory was to the whole body; it directed attention to the individual nerve cell and its processes as a structural and functional unit. Waldeyer (1836—1921) enunciated it in definite terms in 1891, when he said that the nervous system is made up of cells or neurones, each consisting of a cell body and its various processes, "irrespective of their number, length, complexity, character and position", and Sherrington has stated that the study of the cell is one of the three ways of examining the function of the nervous system. The synapse, or surface separating two neurones or their terminations, was a concept of Michael Foster; its study has been greatly developed by Sherrington, and it is one of the chief objects of neurophysiology at the present day to obtain, by indirect methods, some idea of the nature of the processes occurring at the synapse.

Reflex action, etc.

The chief advance in neurophysiology in the nineteenth century was in the study of reflex action, and it may therefore be worth while to consider this in some detail, even though such a course entails an abridged account of the progress made in other directions. In 1811 Charles Bell (1774—1842) made the important discovery that the anterior spinal roots were motor in function, and the posterior roots non-motor. It is very possible, or even probable, that he recognized the posterior roots

as "sensory", but he was not the first to *print* such a view. At any rate, his discovery provided an anatomical basis which had previously been lacking for the separation of the "sensory" and motor parts of involuntary action. In 1821, John Snow, a pupil of Bell, demonstrated the experiment in Paris, and in 1822 Magendie gave definite proof of the "sensory" function of the posterior roots. The Bell-Magendie law, as it is now usually described, was found by later observers to hold good in many other species and it became the basis of "the law of forward direction", one of the chief principles of reflex, as opposed to peripheral nerve, conduction. Bell in 1822 noted that the stimulation of the nerves to a limb separated from the body resulted in an action of the limb, and not in a contraction of all the muscles. In other words, the nerves arranged for an orderly movement by different action on the different classes of muscles in the limb. Mayo, also in this year, attempted to find an experimental basis for the division of muscles into voluntary and involuntary; he noted, incidentally, that all voluntary actions were not necessarily conscious ones. Two years later, he showed that the seventh cranial nerve was motor in function while the fifth was concerned with common sensitivity. In 1823 Bell followed John Hunter and anticipated Johannes Müller (1826) by saying that every nerve gives rise within the mind to its own peculiar sensation whatever the stimulus applied to it, be it pressure, vibration, heat or electricity.

In 1824 Flourens (1794—1867), who had been performing experiments to show the effect of removal of the cerebrum and cerebellum in pigeons, published a

paper on the functions of the nervous system in vertebrates. The properties of the nervous system were, he stated, sensing, willing and perceiving, effected by the brain, co-ordination of movement, effected by the cerebellum, and excitability. Removal of the cerebellum resulted in ataxia. In 1826, the year in which Müller announced his doctrine of specific nerve energies, Bell made two further important statements. First, he said that muscles were supplied with sensory as well as with motor nerves, and that the former conveyed a "sense of the condition of the muscles to the brain" for the regulation of muscular action. Secondly, he spoke of a "circle of nerves" making a sensory-motor junction between brain and muscle. He had, before this year, stated that an "unconscious principle" might also be the centre of a nerve circle, though he did not in so many words localize it in the spinal cord. He came nearer than his predecessors, at any rate, to describing a reflex arc as a medium for the involuntary contraction of muscles.

In 1833 Marshall Hall (1790—1857) published his memoir entitled "*The reflex function of the medulla oblongata and medulla spinalis*"; this and other writings of his, though in many ways perhaps only an elaboration of previous work, yet had the important effect of establishing the concept of reflex action in neurophysiology and in neurological medicine. His chief fault was that he separated too rigidly the idea of reflex and of voluntary movements. In 1833 he said that there were four kinds of muscular contractions: voluntary, effected by the cerebrum by way of the spinal cord and the motor nerves to voluntary muscles; respiratory, effected by the medulla oblongata and the

nerves to certain muscles; involuntary, depending on the innate irritability of the muscle; and his new kind, which ceased on removal of the spinal medulla. The medulla spinalis, by purely reflex function, presided over the sphincters and the tone and equilibrium of certain parts of the muscular system. He made the important observation that the operation of reflex function is not confined to parts corresponding with distinct portions of the spinal medulla. In a memorandum dictated during his last illness he spoke of "reflex, or diastaltic, or diacentric action", so he may be called the originator of the term "reflex action". In 1837 he called the system of nerves subserving reflex function the excito-motory system, a "true spinal system" as distinct from the "cerebral system". He did, however, say that the excito-motory system is susceptible of modification by volition. In the same year Grainger stated that the spinal cord is the sole seat of spinal reflexes, and that the afferent roots involved in reflex action go straight into the grey matter, but he also said that other afferent fibres proceed up in the white matter to the brain for the purpose of sensation. In 1842 Arnold noted that reflexes are dependent upon the quality, intensity, and location of the stimulus. In 1850 Marshall Hall announced that "the anatomy of the diastaltic [reflex] system consists in an esodic nerve [an afferent nerve going into the spinal cord], the spinal centre, and an exodic nerve [an efferent nerve going out of the cord to the muscle], essentially linked together, and constituting a diastaltic nervous arc [the first use of the word 'arc' in this connection]. The physiology of this system consists in such an arc, or such arcs, in diastaltic action".

In 1855 Herbert Spencer stated that reflexes were found only in organisms with a differentiated nervous system, and that a reflex is always initiated in cells specially modified for the reception of stimuli. The year 1863 is important as marking the beginning of ideas of central, as opposed to peripheral, inhibition. The discovery by the brothers Weber, in 1845, of the peripheral inhibitory power of the vagus upon the heart had given a new idea of nerve function, for previously to their announcement all efferent nerves had been regarded as excitatory. After 1845 others had looked for inhibitory nerves, and by 1863 Pflüger had shown that the intestinal movements are lessened on splanchnic stimulation (1857), and Claude Bernard had described the vasodilator action of the chorda tympani (1858). These nerves were, however, visceral and circulatory nerves, the inhibitory effect of which is entirely peripheral. Setschenow in 1863 published a monograph in which he analysed, with the help of experimental data, the idea that the brain is responsible for the inhibitory effects observed in spinal reflexes. He showed such inhibition in frogs and in man, but his method of accounting for it by the postulation of specific inhibitory centres soon raised a storm of objection. Since his time many theories as to the intimate nature of inhibition in reflex action have been propounded, and almost as many have been discarded. Nevertheless, the site of the inhibitory process has been identified, and the elimination of theories as to its nature has no doubt brought us nearer to the true solution of this difficult problem.

In 1870 Fritsch (1838—1891) and Hitzig (1838—1907) inaugurated the physiological study of the

cerebral cortex by experiments which they made on dogs. Before their time there had been no reliable information as to the function of the cortex, and their application to this part of the body of the common physiological methods of extirpation and stimulation was a great step forward. In 1871—1876 appeared Wundt's memoirs on the mechanics of the nerves and nerve centres, in which were discussed such matters as reaction time, the time required for the passage of impulses through the spinal cord and ganglia, and muscle sense. In 1873 David Ferrier (1843—1928) began his epoch-making studies of the nervous system; among other things, he stimulated the motor cortex of mammals, birds, frogs, fishes, etc., and by so doing laid the foundation of our modern concepts of the functions of the brain. Fritsch and Hitzig, in their experiments in 1870, had used the make and break of a constant current as a stimulus; Ferrier employed the faradic current, and this has remained the method of choice ever since. Current views on the cerebrum, before 1870, were that it was the organ of mind, and functioned as a whole; it was also supposed to be inexcitable. It is true that one can find earlier clinical suggestions of something more than this, but it was Ferrier's experimental work which made them anything other than hypotheses, and he therefore deserves the credit.

The "refractory phase" was noted in *Medusa* in 1877, and has since come to mean much in neurophysiology. In 1882 Exner wrote on the "facilitation" of reflexes, and his idea has become incorporated in subsequent work on reflex action. In 1885 Charles Scott Sherrington, who was to give form to the scattered

knowledge of the nervous system in the same way that Haldane was to that of the respiratory system, began his work. Between 1893 and 1909 he elucidated the reciprocal innervation of antagonistic muscles, between 1895 and 1917 he added to our knowledge of the functions of the motor cortex, and between 1898 and 1906 he worked on the levels of nervous integration. In the middle of other work in the nineteenth century, he showed that section through the brain-stem at the level of the corpora quadrigemina leads to "decerebrate rigidity". In 1897 Foster, in his textbook, emphasized a point of view which had been greatly overlooked earlier in the century, and said that the knowledge of function derived from the study of parts of the central nervous system was not likely to give a complete picture; we must not forget in our search after details to remember that the nervous system is a functional entity, and should be considered as such. About 1898 Pavlov commenced the study of conditioned reflexes as a guide to the physiology of the cerebral hemispheres, and in 1899 Jacques Loeb began his work on "chain reflexes".

The autonomic nervous system

Lack of space prevents any adequate description of other advances made during the century, such as the work of Purkinje and Flourens on the semicircular canals, of Weber on the measurement of sensation, of du Bois-Reymond on electrical changes in nerve during activity, of Helmholtz on the measurement of the velocity of the nervous impulse, and of Bowditch on the unfatigability of nerve. But more than a passing word should be written about the work which was done on what Langley later called "the autonomic nervous system".

Sheehan (*Arch. Neurol. Psychiatr.*, 1936, *35*, 1081—1115) can be consulted for the detailed story; in its later and more important stages, the fundamental research was in large measure inaugurated by Gaskell and carried on by Langley (once described as "the only researcher whose conclusions have never been contradicted"), who published nearly seventy papers on the subject between 1890 and his death. To these two Cambridge men we are indebted for some of our main concepts of the control of smooth muscle and glands by the central nervous system.

The special senses

Among the organs of special sense, the eye has always attracted a predominant interest, and it was so during the years under review. Thomas Young put forward his hypothesis of colour vision in 1801, and suggested that the retina contains structures which, on stimulation, give rise to sensations of red, green and violet. Bowman described the ciliary region in 1847, and Donders in the following year explained the relation between convergence of the visual axes and accommodation. In 1852 Joseph Lister confirmed von Kölliker's view that the contractile tissue of the iris is smooth muscle. Helmholtz, during the years from 1853 onwards, elaborated his hypothesis of vision, explained the mechanism of accommodation, and began an exhaustive textbook of physiological optics. Other hypotheses of vision were those of Hering, 1872—1875, and of C. L. Franklin, 1892. Schultze gave an account of the anatomy and physiology of the retina in 1866, and von Kries produced a memoir on the function of the rods in 1874. Hearing was the subject of other publications by Helmholtz (1863, 1869), and several memoirs were written

during the century on the physiology of speech. Smell was studied by Zwaardemaker, who wrote on this subject in 1895.

Muscle

It is not without significance that Scheele had isolated lactic acid in 1780 and that Girtanner, who died in 1800, had bequeathed to Richerand the idea that the cause of muscular contraction is the splitting of chemical substances within the muscle fibre. Richerand published this view in 1800. In 1837 Schwann described the striped muscle of the upper oesophagus and demonstrated that the tension of a contracting muscle varies with its length. In 1838 Matteuci (1811—1868) noted muscle currents, though he did not appreciate their significance. In 1840 and 1841 Bowman wrote on the minute structure and movements of voluntary muscle, and provided illustrations of striated muscle which were drawn by himself. In the following year Müller gave du Bois-Reymond Matteuci's paper on frog currents, and in 1842 Matteuci himself described "secondary contraction" of muscle. Du Bois-Reymond (1818—1896) found, in 1843, that there is a current of rest in muscle, and that it diminishes during activity. Helmholtz occupied himself in 1845 with experiments on the chemical changes occurring in frog's muscle during its contraction, and in 1848 came to the conclusion that muscles are the main source of animal heat. In his research he used a thermocouple for the first time for measuring the heat production of isolated muscles. The same year was also marked by the publication of the first volume of du Bois-Reymond's *Untersuchungen über thierische Elektricität* (Researches on animal electricity). In this great work were included details of further research on the negative

variation of active muscle, and the statement that tetanized muscle is acid in reaction, while resting muscle is neutral. Liebig synthesized lactic acid in 1850, and in the same year Helmholtz said that muscular contraction results in the formation of an acid substance; Claude Bernard also began his research on the action of curare, which was to give a definite proof that muscle can be excited independently of its nerve. As Bernard was finishing with curare six years later, von Kölliker was beginning the study of the veratrinized muscle. Wundt also did valuable research on the action of drugs upon muscle, and published an important memoir on muscular contraction in 1858.

The first definite association of carbohydrate metabolism with muscular contraction was made by Fick (1829—1901) in 1867. Four years later Kronecker wrote on fatigue and recovery in striped muscle, and announced that the acid formed during muscular contraction was the same as that found in sour milk. Claude Bernard, however, in 1877 said that lactic acid was not the cause of rigor, but only its *usual* accompaniment. Had his observation been remembered and appreciated, it would have accelerated the determination of the more essential processes of muscle metabolism during the present century. But it was, unfortunately, forgotten or ignored by later workers. In 1882 Fick published a memoir on mechanical work and heat production during muscular activity; in this he correlated the mechanical conditions with the liberation of heat, but he did not distinguish clearly the various phases of heat production. He did, however, prove that in muscle chemical energy is transferred directly into work without passing through an intermediate stage of heat.

In 1893 Gad put forward the hypothesis that lactic acid is the cause of muscular contraction, and that after contraction has been effected this substance is oxidized with liberation of heat. Five years later, Fletcher initiated the modern development of the subject with his paper on "The survival respiration of muscle".

Embryology, etc.

It is to von Baer (1792—1876) that we owe the first important advances in embryology in the century. He described his discovery of the mammalian ovum in 1827, and by his history of animal development, 1828—37, he made embryology a comparative science. He was primarily responsible for the "germ-layer theory", though he thought there were four layers of tissue developed from the division of the ovum; each layer, as he noticed, gives rise to the same organs over a wide range of species. In 1829 Rathke described the gill slits and arches in embryos of birds and mammals. Von Kölliker (1843) was one of the first to apply the new cell theory to embryological descriptions. In 1845 Remak showed that there are three germ-layers, ectoderm, endoderm and mesoderm, and not four, as noted by von Baer. Von Kölliker, in 1847, demonstrated the development of spermatozoa, and in the following year Leydig described the division of the nuclei which occurs during the segmentation of the ovum. Von Kölliker's textbook (1861) was the first general account of embryology on a cellular basis. In our own country the chief books on the subject were Foster and Balfour's *Elements of Embryology*, 1874, and Balfour's great *Comparative Embryology*, 1880—81. In 1824 Prévost and Dumas corrected Spallanzani's mistake and proved that it is the spermatozoa which fertilize, not the seminal fluid;

in 1879 Hermann Fol saw, for the first time, a spermatozoon penetrate an ovum. Weissmann in 1885 differentiated the continuing character of germ-cells from the transitory character of body cells, and Boveri in 1891 initiated modern views of spermatogenesis and oögenesis. Finally, the idea of a spontaneous generation of micro-organisms came to an end when Pasteur published his memoir of 1861; henceforward the motto was to be "*Omne vivum e vivo*".

The alimentary canal

A certain amount of research, other than has already been described, was done on the alimentary canal. Ludwig described the movements of the intestines in 1861, and stated that the pendular contractions occur in the intervals of peristalsis; in 1874 Goltz found that the rectum could act independently of the nervous system; and about 1888 Heidenhain began a long series of investigations of the chemistry and histology of intestinal absorption. Mall showed in 1896 that, if a piece of intestine is cut out and reversed, obstruction will result. Cannon initiated much subsequent research when he used X-rays in 1898 to study the normal gastric movements; some of his original sketches are preserved in the Institute of Physiology, University College, London. In 1899 Bayliss and Starling showed, apparently, that peristalsis is a movement effected through the intrinsic ganglia of the intestine.

Enzymes

Mention has already been made of various enzymes that were discovered and named, so it is only necessary to note here a few general advances. Fischer pointed out the specificity of enzymes in 1894, and three years later Bertrand wrote on co-enzymes. "The possibility that a chemical combin-

ation between enzyme and substrate led to the phenomenon of enzymic specificity was first suggested by Emil Fischer" in 1898—99. "The modern conception of enzyme action, which has already withstood considerable experimental testing, is, in its essential features, a continuation of the thought of Emil Fischer" (Waldschmidt-Leitz, 1931).

EPILOGUE

We have now studied, however briefly, the progress of physiological research and thought over a period of two thousand five hundred years. We may close with a brief description of Claude Bernard's idea of the internal environment, upon the constancy of which, he stated, the free life of the higher animals depends. Such animals may be placed in very variable external environments, but the effects of these are all neutralized by various mechanisms, so that the internal environment (the lymph or plasma), in which the essential units of the body (the tissue cells) live, may remain for all practical purposes unchanged in its composition and in its physico-chemical properties. Water, oxygen, heat, and reserve chemical substances are taken up by the circulating fluid in due amount to maintain the constancy of the internal environment, and the nervous system presides over the whole, further to safeguard the harmonious existence of the tissue cells and to co-ordinate their activities.

INDEX OF PERSONAL NAMES

(The sectional headings within the chapters are a quick guide to *subjects* in the seventeenth, eighteenth, and nineteenth centuries.)